

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
5 December 2002 (05.12.2002)

PCT

(10) International Publication Number
WO 02/096907 A1

(51) International Patent Classification⁷: **C07D 471/04**,
A61P 31/00

New Frontiers Science Park South, Third Avenue, Harlow,
Essex CM19 5AW (GB).

(21) International Application Number: PCT/EP02/05709

(74) Agent: **VALENTINE, Jill, Barbara**; Corporate Intellectual Property, GlaxoSmithKline, 980 Great West Road, Brentford, Middlesex TW8 9GS (GB).

(22) International Filing Date: 24 May 2002 (24.05.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0112836.2 25 May 2001 (25.05.2001) GB

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(71) Applicant (*for all designated States except US*):
SMITHKLINE BEECHAM P.L.C. [GB/GB]; 980 Great West Road, Brentford, Middlesex TW8 9GS (GB).

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **DARTOIS, Catherine, Genevieve, Yvette** [FR/FR]; Laboratoire GlaxoSmithKline S.A.S., 100 Route de Versailles, F-78163 Marly-le-Roi Cedex (FR). **MARKWELL, Roger, Edward** [GB/GB]; GlaxoSmithKline, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). **MADLER, Guy, Marguerite, Marie, Gerard** [FR/FR]; Laboratoire GlaxoSmithKline S.A.S., 100 Route de Versailles, F-78163 Marly-le-Roi Cedex (FR). **PEARSON, Neil, David** [GB/GB]; GlaxoSmithKline,

Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/096907 A1

(54) Title: BICYCLIC NITROGEN-CONTAINING HETEROCYCLIC DERIVATIVES FOR USE AS ANTIBACTERIALS

(57) Abstract: Piperidine derivatives and pharmaceutically acceptable derivatives thereof useful in methods of treatment of bacterial infections in mammals, particularly man.

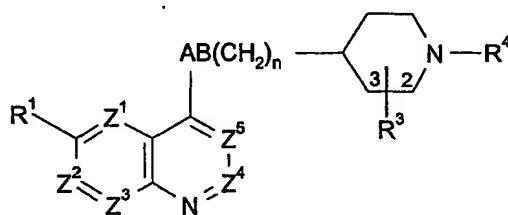
BICYCLIC NITROGEN-CONTAINING HETEROCYCLIC DERIVATIVES FOR USE AS ANTIBACTERIALS

This invention relates to novel compounds, compositions containing them and their use as antibacterials.

5 WO099/37635, WO00/21948, WO0021952, WO00/43383, WO0078748, WO01/07433, WO01/07432, WO02/08224, WO02/24684 and WO01/25227 disclose piperidine and piperazine derivatives having antibacterial activity.

This invention provides a compound of formula (I) or a pharmaceutically acceptable derivative thereof:

10



(I)

wherein:

15

one of Z¹, Z², Z³, Z⁴ and Z⁵ is N, one is CR^{1a} and the remainder are CH, or one of Z¹, Z², Z³, Z⁴ and Z⁵ is CR^{1a} and the remainder are CH;

R¹ and R^{1a} are independently selected from hydrogen; hydroxy; (C₁₋₆) alkoxy optionally substituted by (C₁₋₆)alkoxy, amino, piperidyl, guanidino or amidino any of which is optionally N-substituted by one or two (C₁₋₆)alkyl, acyl or (C₁₋₆)alkylsulphonyl groups, CONH₂, hydroxy, (C₁₋₆)alkylthio, heterocyclylthio, heterocycloxy, arylthio, aryloxy, acylthio, acyloxy or (C₁₋₆)alkylsulphonyloxy; (C₁₋₆)alkoxy-substituted (C₁₋₆)alkyl; halogen; (C₁₋₆)alkyl; (C₁₋₆)alkylthio; trifluoromethyl; nitro; azido; acyl; acyloxy; acylthio; (C₁₋₆)alkylsulphonyl; (C₁₋₆)alkylsulphoxide; arylsulphonyl; arylsulphoxide or an amino, piperidyl, guanidino or amidino group optionally N-substituted by one or two (C₁₋₆)alkyl, acyl or (C₁₋₆)alkylsulphonyl groups, or when Z¹ is CR^{1a}, R¹ and R^{1a} may together represent (C₁₋₂)alkylenedioxy, provided that when Z¹, Z², Z³, Z⁴ and Z⁵ are CR^{1a} or CH, then R¹ is not hydrogen;

30

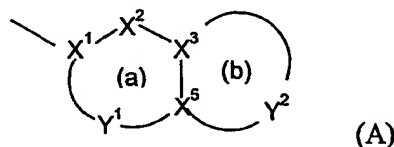
R³ is hydrogen; or

R³ is in the 2- or 3-position and is:

- carboxy; (C₁₋₆)alkoxycarbonyl; aminocarbonyl wherein the amino group is optionally substituted by hydroxy, (C₁₋₆)alkyl, hydroxy(C₁₋₆)alkyl, aminocarbonyl(C₁₋₆)alkyl, (C₂₋₆)alkenyl, (C₁₋₆)alkylsulphonyl, trifluoromethylsulphonyl, (C₂₋₆)alkenylsulphonyl, (C₁₋₆)alkoxycarbonyl, (C₁₋₆)alkylcarbonyl, (C₂₋₆)alkenyloxycarbonyl or (C₂₋₆)alkenylcarbonyl and optionally further substituted by (C₁₋₆)alkyl, hydroxy(C₁₋₆)alkyl, aminocarbonyl(C₁₋₆)alkyl or (C₂₋₆)alkenyl; cyano; tetrazolyl; 2-oxo-oxazolidinyl optionally substituted by R¹⁰; 3-hydroxy-3-cyclobutene-1,2-dione-4-yl; 2,4-thiazolidinedione-5-yl; tetrazol-5-ylaminocarbonyl; 1,2,4-triazol-5-yl optionally substituted by R¹⁰; or 5-oxo-1,2,4-oxadiazol-3-yl; or
- (C₁₋₄)alkyl or ethenyl optionally substituted with any of the groups listed above for R³ and/or 0 to 2 groups R¹² independently selected from:
- halogen; (C₁₋₆)alkylthio; trifluoromethyl; (C₁₋₆)alkoxycarbonyl; (C₁₋₆)alkylcarbonyl; (C₂₋₆)alkenyloxycarbonyl; (C₂₋₆)alkenylcarbonyl; hydroxy optionally substituted by (C₁₋₆)alkyl, (C₂₋₆)alkenyl, (C₁₋₆)alkoxycarbonyl, (C₁₋₆)alkylcarbonyl, (C₂₋₆)alkenyloxycarbonyl, (C₂₋₆)alkenylcarbonyl or aminocarbonyl wherein the amino group is optionally substituted by (C₁₋₆)alkyl, (C₂₋₆)alkenyl, (C₁₋₆)alkylcarbonyl or (C₂₋₆)alkenylcarbonyl; amino optionally mono- or disubstituted by (C₁₋₆)alkoxycarbonyl, (C₁₋₆)alkylcarbonyl, (C₂₋₆)alkenyloxycarbonyl, (C₂₋₆)alkenylcarbonyl, (C₁₋₆)alkyl, (C₂₋₆)alkenyl, (C₁₋₆)alkylsulphonyl, (C₂₋₆)alkenylsulphonyl or aminocarbonyl wherein the amino group is optionally substituted by (C₁₋₆)alkyl, hydroxy(C₁₋₆)alkyl, aminocarbonyl(C₁₋₆)alkyl, (C₂₋₆)alkenyl, (C₁₋₆)alkoxycarbonyl, (C₁₋₆)alkylcarbonyl, (C₂₋₆)alkenyloxycarbonyl or (C₂₋₆)alkenylcarbonyl and optionally further substituted by (C₁₋₆)alkyl, hydroxy(C₁₋₆)alkyl, aminocarbonyl(C₁₋₆)alkyl or (C₂₋₆)alkenyl; oxo; (C₁₋₆)alkylsulphonyl; (C₂₋₆)alkenylsulphonyl; or (C₁₋₆)aminosulphonyl wherein the amino group is optionally substituted by (C₁₋₆)alkyl or (C₂₋₆)alkenyl; or
- when R³ is in the 3-position it may instead be selected from hydroxy optionally substituted by (C₁₋₆)alkyl, (C₂₋₆)alkenyl, (C₁₋₆)alkoxycarbonyl, (C₁₋₆)alkylcarbonyl, (C₂₋₆)alkenyloxycarbonyl, (C₂₋₆)alkenylcarbonyl or aminocarbonyl wherein the amino group is optionally substituted by (C₁₋₆)alkyl, (C₂₋₆)alkenyl, (C₁₋₆)alkylcarbonyl or (C₂₋₆)alkenylcarbonyl, and amino optionally mono- or disubstituted by (C₁₋₆)alkoxycarbonyl, (C₁₋₆)alkylcarbonyl, (C₂₋₆)alkenyloxycarbonyl, (C₂₋₆)alkenylcarbonyl, (C₁₋₆)alkyl, (C₂₋₆)alkenyl, (C₁₋₆)alkylsulphonyl, (C₂₋₆)alkenylsulphonyl or aminocarbonyl wherein the amino group is optionally substituted by (C₁₋₆)alkyl or (C₂₋₆)alkenyl;

in addition when R^3 is disubstituted with a hydroxy or amino containing substituent and a carboxy containing substituent these may optionally together form a cyclic ester or amide linkage, respectively;

- 5 R^{10} is selected from (C₁₋₄)alkyl; (C₂₋₄)alkenyl and aryl any of which may be optionally substituted by a group R^{12} as defined above; carboxy; aminocarbonyl wherein the amino group is optionally substituted by hydroxy, (C₁₋₆)alkyl, (C₂₋₆)alkenyl, (C₁₋₆)alkylsulphonyl, trifluoromethylsulphonyl, (C₂₋₆)alkenylsulphonyl, (C₁₋₆)alkoxycarbonyl, (C₁₋₆)alkylcarbonyl, (C₂₋₆)alkenyloxycarbonyl or (C₂₋₆)alkenylcarbonyl and optionally further substituted by (C₁₋₆)alkyl or (C₂₋₆)alkenyl; (C₁₋₆)alkylsulphonyl; trifluoromethylsulphonyl; (C₂₋₆)alkenylsulphonyl; (C₁₋₆)alkoxycarbonyl; (C₁₋₆)alkylcarbonyl; (C₂₋₆)alkenyloxycarbonyl; and (C₂₋₆)alkenylcarbonyl;
- 10 R^4 is a group -U-V- R^5 where R^5 is an optionally substituted bicyclic carbocyclic or heterocyclic ring system (A):



containing up to four heteroatoms in each ring in which

at least one of rings (a) and (b) is aromatic;

- 20 X^1 is C or N when part of an aromatic ring or CR^{14} or N when part of a non aromatic ring;

X^2 is N, NR^{13} , O, $S(O)_x$, CO or CR^{14} when part of an aromatic or non-aromatic ring or may in addition be $CR^{14}R^{15}$ when part of a non aromatic ring;

X^3 and X^5 are independently N or C;

- 25 Y^1 is a 0 to 4 atom linker group each atom of which is independently selected from N, NR^{13} , O, $S(O)_x$, CO and CR^{14} when part of an aromatic or non-aromatic ring or may additionally be $CR^{14}R^{15}$ when part of a non aromatic ring,

- Y^2 is a 2 to 6 atom linker group, each atom of Y^2 being independently selected from N, NR^{13} , O, $S(O)_x$, CO and CR^{14} when part of an aromatic or non-aromatic ring or may additionally be $CR^{14}R^{15}$ when part of a non aromatic ring;

- 30 each of R^{14} and R^{15} is independently selected from: H; (C₁₋₄)alkylthio; halo; carboxy(C₁₋₄)alkyl; halo(C₁₋₄)alkoxy; halo(C₁₋₄)alkyl; (C₁₋₄)alkyl; (C₂₋₄)alkenyl; (C₁₋₄)alkoxycarbonyl; formyl; (C₁₋₄)alkylcarbonyl; (C₂₋₄)alkenyloxycarbonyl; (C₂₋₄)alkenylcarbonyl; (C₁₋₄)alkylcarbonyloxy; (C₁₋₄)alkoxycarbonyl(C₁₋₄)alkyl; hydroxy; hydroxy(C₁₋₄)alkyl; mercapto(C₁₋₄)alkyl; (C₁₋₄)alkoxy; nitro; cyano; carboxy; amino or

aminocarbonyl optionally substituted as for corresponding substituents in R³; (C₁₋₄)alkylsulphonyl; (C₂₋₄)alkenylsulphonyl; or aminosulphonyl wherein the amino group is optionally substituted by (C₁₋₄)alkyl or (C₂₋₄)alkenyl; aryl; aryl(C₁₋₄)alkyl; aryl(C₁₋₄)alkoxy;

- 5 each R¹³ is independently hydrogen, trifluoromethyl; (C₁₋₄)alkyl optionally substituted by hydroxy, carboxy, (C₁₋₆)alkoxycarbonyl, (C₁₋₆)alkoxy, (C₁₋₆)alkylthio, halo or trifluoromethyl; (C₂₋₄)alkenyl; aryl; aryl (C₁₋₄)alkyl; arylcarbonyl; heteroarylcarbonyl; (C₁₋₄)alkoxycarbonyl; (C₁₋₄)alkylcarbonyl; formyl; (C₁₋₆)alkylsulphonyl; or aminocarbonyl wherein the amino group is optionally substituted by
 10 (C₁₋₄)alkoxycarbonyl, (C₁₋₄)alkylcarbonyl, (C₂₋₄)alkenyloxycarbonyl, (C₂₋₄)alkenylcarbonyl, (C₁₋₄)alkyl or (C₂₋₄)alkenyl and optionally further substituted by (C₁₋₄)alkyl or (C₂₋₄)alkenyl;

each x is independently 0, 1 or 2;

- U is CO, SO₂ or CH₂ and V is CR¹⁷R¹⁸ or U is CH₂ and V is CO, SO₂ or CR¹⁷R¹⁸;
 15

- R¹⁷ and R¹⁸ are independently selected from hydrogen, hydroxy optionally substituted by (C₁₋₆)alkyl, (C₂₋₆)alkenyl, (C₁₋₆)alkoxycarbonyl, (C₁₋₆)alkylcarbonyl, (C₂₋₆)alkenyloxycarbonyl, (C₂₋₆)alkenylcarbonyl or aminocarbonyl wherein the amino group is optionally substituted by (C₁₋₆)alkyl, (C₂₋₆)alkenyl, (C₁₋₆)alkylcarbonyl or (C₂₋₆)alkenylcarbonyl; and amino optionally mono- or disubstituted by (C₁₋₆)alkoxycarbonyl,
 20 (C₁₋₆)alkylcarbonyl, (C₂₋₆)alkenyloxycarbonyl, (C₂₋₆)alkenylcarbonyl, (C₁₋₆)alkyl, (C₂₋₆)alkenyl, (C₁₋₆)alkylsulphonyl, (C₂₋₆)alkenylsulphonyl or aminocarbonyl wherein the amino group is optionally substituted by (C₁₋₆)alkyl or (C₂₋₆)alkenyl;

- 25 n is 0 or 1 and AB is NR¹¹CO, CONR¹¹, CO-CR⁸R⁹, CR⁶R⁷-CO, O-CR⁸R⁹, CR⁶R⁷-O, NHR¹¹-CR⁸R⁹, CR⁶R⁷-NHR¹¹, NR¹¹SO₂, CR⁶R⁷-SO₂ or CR⁶R⁷-CR⁸R⁹; or n is 0 or 1 and AB is NH-CO-NH or NH-CO-O;
 or n is 0 and AB is CR⁶R⁷SO₂NR¹¹, CR⁶R⁷CONR¹¹ or CR⁶R⁷CH₂NR¹¹;
 provided that R⁶ and R⁷, and R⁸ and R⁹ are not both optionally substituted hydroxy or
 30 amino;

and wherein:

- each of R⁶, R⁷, R⁸ and R⁹ is independently selected from: H; (C₁₋₆)alkoxy; (C₁₋₆)alkylthio; halo; trifluoromethyl; azido; (C₁₋₆)alkyl; (C₂₋₆)alkenyl; (C₁₋₆)alkoxycarbonyl; (C₁₋₆)alkylcarbonyl; (C₂₋₆)alkenyloxycarbonyl; (C₂₋₆)alkenylcarbonyl; hydroxy, amino or aminocarbonyl optionally substituted as for
 35 corresponding substituents in R³; (C₁₋₆)alkylsulphonyl; (C₂₋₆)alkenylsulphonyl; or (C₁₋

6)aminosulphonyl wherein the amino group is optionally substituted by (C₁₋₆)alkyl or (C₂₋₆)alkenyl;
or R⁶ and R⁸ together represent a bond and R⁷ and R⁹ are as above defined;

- 5 and each R¹¹ is independently H; trifluoromethyl; (C₁₋₆)alkyl; (C₂₋₆)alkenyl; (C₁₋₆)alkoxycarbonyl; (C₁₋₆)alkylcarbonyl; or aminocarbonyl wherein the amino group is optionally substituted by (C₁₋₆)alkoxycarbonyl, (C₁₋₆)alkylcarbonyl, (C₂₋₆)alkenyloxycarbonyl, (C₂₋₆)alkenylcarbonyl, (C₁₋₆)alkyl or (C₂₋₆)alkenyl and optionally further substituted by (C₁₋₆)alkyl or (C₂₋₆)alkenyl;
- 10 or where one of R³ and R⁶, R⁷, R⁸ or R⁹ contains a carboxy group and the other contains a hydroxy or amino group they may together form a cyclic ester or amide linkage.

The invention also provides the use of a compound of formula (I) or a
15 pharmaceutically acceptable derivative thereof in the manufacture of a medicament for use in the treatment of bacterial infections in mammals.

The invention also provides a pharmaceutical composition, in particular for use in the treatment of bacterial infections in mammals, comprising a compound of formula (I), or a pharmaceutically acceptable derivative thereof, and a pharmaceutically acceptable
20 carrier.

The invention further provides a method of treatment of bacterial infections in mammals, particularly in man, which method comprises the administration to a mammal in need of such treatment of an effective amount of a compound of formula (I), or a pharmaceutically acceptable derivative thereof.

25 In one aspect, when (a) and (b) are both aromatic, -U-V- is not -CH₂-CO- or -(CH₂)₂-. In another aspect when -U-V- is -CH₂-CO- or -(CH₂)₂-, R⁵ is not indolyl, quinolinyl or benzothienyl.

In a further aspect n=0, R¹ and R^{1a} do not together represent (C₁₋₂)alkylenedioxy, and R¹³ does not represent carboxy or (C₁₋₆)alkoxycarbonyl.
30

Preferably Z⁵ is CH or N, Z³ is CH or CF and Z¹, Z² and Z⁴ are each CH, or Z¹ is N, Z³ is CH or CF and Z², Z⁴ and Z⁵ are each CH.

When R¹ or R^{1a} is substituted alkoxy it is preferably (C₂₋₆)alkoxy substituted by optionally N-substituted amino, guanidino or amidino, or (C₁₋₆)alkoxy substituted by
35 piperidyl. Suitable examples of R¹ alkoxy include methoxy, trifluoromethoxy, n-propyloxy, i-butyloxy, aminoethyloxy, aminopropyloxy, aminobutyloxy, aminopentyloxy, guanidinopropyloxy, piperidin-4-ylmethyloxy, phthalimido pentyloxy or 2-

aminocarbonylprop-2-oxy. Preferably R^1 is methoxy, amino(C₃₋₅)alkyloxy, guanidino(C₃₋₅)alkyloxy, piperidyl(C₃₋₅)alkyloxy, nitro or fluoro.

Preferably R^1 and R^{1a} are independently methoxy, amino(C₃₋₅)alkyloxy, guanidino(C₃₋₅)alkyloxy, piperidyl(C₃₋₅)alkyloxy, nitro or fluoro; more preferably methoxy, amino(C₃₋₅)alkyloxy or guanidino(C₃₋₅)alkyloxy. Preferably R^{1a} is H or F. Most preferably R^1 is methoxy and R^{1a} is H or when Z^3 is CR^{1a} it may be C-F.

When Z^5 is CR^{1a} , R^{1a} is preferably hydrogen, cyano, hydroxymethyl or carboxy, most preferably hydrogen.

Preferably n is 0.

Preferred examples of R^3 include hydrogen; optionally substituted hydroxy; (C₁₋₄) alkyl; ethenyl; optionally substituted 1-hydroxy-(C₁₋₄) alkyl; optionally substituted aminocarbonyl; carboxy(C₁₋₄)alkyl; optionally substituted aminocarbonyl(C₁₋₄)alkyl; cyano(C₁₋₄)alkyl; optionally substituted 2-oxo-oxazolidinyl and optionally substituted 2-oxo-oxazolidinyl(C₁₋₄alkyl). More preferred R^3 groups are hydrogen; CONH₂; 1-hydroxyalkyl e.g. CH₂OH, CH(OH)CH₂CN; CH₂CO₂H; CH₂CONH₂; -CONHCH₂CONH₂; 1,2-dihydroxyalkyl e.g. CH(OH)CH₂OH; CH₂CN; 2-oxo-oxazolidin-5-yl and 2-oxo-oxazolidin-5-yl(C₁₋₄alkyl). Most preferably R^3 is hydrogen or hydroxy.

When R^3 and R^6 , R^7 , R^8 or R^9 together form a cyclic ester or amide linkage, it is preferred that the resulting ring is 5-7 membered. It is further preferred that the group A or B which does not form the ester or amide linkage is CH₂.

When A is CH(OH) the R-stereochemistry is preferred.

Preferably A is NH, NCH₃, CH₂, CHOH, CH(NH₂), C(Me)(OH) or CH(Me).

Preferably B is CH₂ or CO.

Preferably n=0.

Most preferably:

n is 0 and either A is CHOH or CH₂ and B is CH₂ or A is NH and B is CO.

Preferably R^{11} is hydrogen or (C₁₋₄)alkyl e.g. methyl, more preferably hydrogen.

A preferred subgroup of compounds is where $AB(CH_2)_n$ is NHCO and Z^1 is N.

The group -U-V- is preferably -(CH₂)₂-, CH₂CH(OH) or CH₂CO.

Preferably R^5 is a heterocyclic ring (A) having 8-11 ring atoms including 2-4 heteroatoms of which at least one is N or NR¹³.

Preferably the heterocyclic ring (A) has ring (a) aromatic selected from optionally substituted benzo and pyrido and ring (b) non-aromatic in which preferably Y^2 has 3-5 atoms including a heteroatom bonded to X^5 selected from O, S or NR¹³, where R^{13} is other than hydrogen, and NHCO bonded via N to X^3 , or O bonded to X^3 ; or ring (a) is

aromatic and (b) is aromatic in which preferably Y² contains 2-3 heteroatoms, one of which is S and 1-2 are N, with one N bonded to X³.

Examples of rings (A) include optionally substituted:

5 (a) and (b) aromatic

1H-pyrrolo[2,3-b]-pyridin-2-yl, 1H-pyrrolo[3,2-b]-pyridin-2-yl, 3H-imidazo[4,5-b]-pyridin-2-yl, 3H-quinazolin-4-one-2-yl, benzimidazol-2-yl, benzo[1,2,3]-thiadiazol-5-yl, benzo[1,2,5]thiadiazol-5-yl, benzo[1,2,5]-oxadiazol-5-yl, benzofur-2-yl, benzothiazol-2-yl, benzo[b]thiophen-2-yl, benzoxazol-2-yl, chromen-4-one-3-yl, imidazo[1,2-a]pyridin-2-yl, imidazo-[1,2-a]-pyrimidin-2-yl, indol-2-yl, indol-6-yl, isoquinolin-3-yl, [1,8]-naphthyridine-3-yl, oxazolo[4,5-b]-pyridin-2-yl, quinolin-2-yl, quinolin-3-yl, quinoxalin-2-yl, indan-2-yl, naphthalen-2-yl, 1,3-dioxo-isoindol-2-yl, benzimidazol-2-yl, benzothiophen-2-yl, 1H-benzotriazol-5-yl, 1H-indol-5-yl, 3H-benzooxazol-2-one-6-yl, 3H-benzooxazol-2-thione-6-yl, 3H-benzothiazol-2-one-5-yl, 3H-quinazolin-4-one-2-yl, 3H-quinazolin-4-one-6-yl, 4-oxo-4H-pyrido[1,2-a]pyrimidin-3-yl, benzo[1,2,3]thiadiazol-6-yl, benzo[1,2,5]thiadiazol-5-yl, benzo[1,4]oxazin-2-one-3-yl, benzothiazol-5-yl, benzothiazol-6-yl, cinnolin-3-yl, imidazo[1,2-a]pyridazin-2-yl, imidazo[1,2-b]pyridazin-2-yl, pyrazolo[1,5-a]pyrazin-2-yl, pyrazolo[1,5-a]pyridin-2-yl, pyrazolo[1,5-a]pyrimidin-6-yl, pyrazolo[5,1-c][1,2,4]triazin-3-yl, pyrido[1,2-a]pyrimidin-4-one-2-yl, pyrido[1,2-a]pyrimidin-4-one-3-yl, quinazolin-2-yl, quinoxalin-6-yl, thiazolo[3,2-a]pyrimidin-5-one-7-yl, thiazolo[5,4-b]pyridin-2-yl, thieno[3,2-b]pyridin-6-yl, 3H-benzoxazol-2-one-5-yl, 4-oxo-4H-pyrido[1,2-a]pyrimidin-2-yl, 1-oxo-1,2-dihydro-isoquinolin-3-yl, thiazolo[4,5-b]pyridin-5-yl, [1,2,3]thiadiazolo[5,4-b]pyridin-6-yl and 2H-isoquinolin-1-one-3-yl.

25 (a) is non aromatic

(2S)-2,3-dihydro-1H-indol-2-yl, (2S)-2,3-dihydro-benzo[1,4]dioxine-2-yl, 3-(R,S)-3,4-dihydro-2H-benzo[1,4]thiazin-3-yl, 3-(R)-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-3-yl, 3-(S)-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-3-yl, 2,3-dihydro-benzo[1,4]dioxan-2-yl, 3-substituted-3H-quinazolin-4-one-2-yl, 1-oxo-1,3,4,5-tetrahydrobenzo[c]azepin-2-yl.

30

(b) is non aromatic

1,1,3-Trioxo-1,2,3,4-tetrahydro-1H⁶-benzo[1,4]thiazin-6-yl, benzo[1,3]dioxol-5-yl, 4H-benzo[1,4]oxazin-3-one-6-yl, 2,3-dihydro-benzo[1,4]dioxin-6-yl, 2-oxo-2,3-dihydro-benzoxazol-6-yl, 4H-benzo[1,4]oxazin-3-one-6-yl (3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl), 4H-benzo[1,4]thiazin-3-one-6-yl (3-oxo-3,4-dihydro-2H-benzo[1,4]thiazin-6-yl), 4H-benzo[1,4]oxazin-3-one-7-yl, 4-oxo-2,3,4,5-tetrahydro-benzo[b][1,4]thiazepine-7-yl, 5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyrimidin-6-yl,

35

- benzo[1,3]dioxol-5-yl, 2-oxo-2,3-dihydro-1H-pyrido[2,3-b][1,4]thiazin-7-yl, 2-oxo-2,3-dihydro-1H-pyrido[3,4-b][1,4]thiazin-7-yl, 3-oxo-3,4-dihydro-2H-2-oxo-2,3-dihydro-1H-pyrido[2,3-b]thiazin-7-yl, pyrido[3,2-b][1,4]thiazin-6-yl, 2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-6-yl, 2,3-dihydro-[1,4]dioxino[2,3-c]pyridin-7-yl, 2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-7-yl, [1,2,3]thiadiazolo[5,4-b]pyridin-6-yl.
- 6,7-dihydro-[1,4]dioxino[2,3-d]pyrimidin-2-yl, 3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-yl, 2-oxo-2,3-dihydro-1H-pyrido[3,4-b][1,4]oxazin-7-yl, 2-oxo-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazin-7-yl, 6-oxo-6,7-dihydro-5H-8-thia-1,2,5-triazanaphthalen-3-yl, 3,4-dihydro-2H-benzo[1,4]oxazin-6-yl, 3,4-dihydro-2H-benzo[1,4]oxazin-6-yl, 3-substituted-3H-benzooxazol-2-one-6-yl, 3-substituted-3H-benzooxazole-2-thione-6-yl, 3-substituted-3H-benzothiazol-2-one-6-yl, 2,3-dihydro-1H-pyrido[2,3-b][1,4]thiazin-7-yl, 3,4-dihydro-2H-benzo[1,4]thiazin-6-yl, 3,4-dihydro-1H-quinolin-2-one-7-yl, 3,4-dihydro-1H-quinoxalin-2-one-7-yl, 6,7-dihydro-4H-pyrazolo[1,5-a]pyrimidin-5-one-2-yl, 5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl, 2-oxo-3,4-dihydro-1H-[1,8]naphthyridin-6-yl.

R¹³ is preferably H if in ring (a) or in addition (C₁₋₄)alkyl such as methyl or isopropyl when in ring (b). More preferably, in ring (b) R¹³ is H when NR¹³ is bonded to X³ and (C₁₋₄)alkyl when NR¹³ is bonded to X⁵.

- R¹⁴ and R¹⁵ are preferably independently selected from hydrogen, halo, hydroxy, (C₁₋₄)alkyl, (C₁₋₄)alkoxy, trifluoromethoxy, nitro, cyano, aryl(C₁₋₄)alkoxy and (C₁₋₄)alkylsulphonyl.

More preferably R¹⁵ is hydrogen.

- More preferably each R¹⁴ is selected from hydrogen, chloro, fluoro, hydroxy, methyl, methoxy, trifluoromethoxy, benzyloxy, nitro, cyano and methylsulphonyl. Most preferably R¹⁴ is selected from hydrogen, hydroxy, fluorine or nitro. Preferably 0-3 groups R¹⁴ are substituents other than hydrogen.

Most preferably R¹⁴ and R¹⁵ are each H.

Most preferred groups R⁵ include:

- 3-oxo-3,4-dihydro-2H-benzo[1,4]thiazin-6-yl (4H-benzo[1,4] thiazin-3-one-6-yl)
benzo[1,3]dioxol-5-yl
2,3-Dihydro-benzo[1,4]dioxin-6-yl
4-fluorobenzimidazol-2-yl
benzo[1,2,5]thiadiazol-5-yl
3-methyl-2-oxo-2,3-dihydro-benzooxazol-6-yl
3H-benzoxazol-2-one-5-yl
quinoxalin-2-yl

- [1,2,3]thiadiazolo[5,4-b]pyridin-6-yl
- 2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-7-yl
- 2,3-Dihydro-[1,4]dioxino[2,3-c]pyridin-7-yl
- 2-oxo-2,3-dihydro-1H-pyrido[2,3-b][1,4]thiazin-7-yl
- 5 3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl (4H-benzo[1,4]oxazin-3-one-6-yl)
- 3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-yl
- 6-nitro-benzo[1,3]dioxol-5-yl
- 7-fluoro-3-oxo-3,4-dihydro-2H-benzo[1,4] oxazin-6-yl
- benzo[1,2,3]thiadiazol-5-yl
- 10 4,6-difluoro-indol-2-yl,
- 1H-pyrrolo[2,3-b]-pyridin-2-yl,
- 1H-pyrrolo[3,2-b]-pyridin-2-yl,
- 8-hydroxy-quinolin-2-yl,
- 5-fluorobenzimidazol-2-yl,
- 15 benzothiophen-2-yl,
- 4,6-difluoro-1H-benzimidazol-2-yl,
- 2,2-difluoro-benzo[1,3]dioxol-5-yl,
- 6-chloro-benzo[1,3]dioxol-5-yl,
- 2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-6-yl
- 20 3,4-dihydro-2H-benzo[1,4]oxazin-6-yl
- 4-oxo-4H-pyrido[1,2-a]pyrimidin-2-yl
- 8-Hydroxy-1-oxo-1,2-dihydro-isoquinolin-3-yl
- benzothiazol-5-yl
- thiazolo-[5,4-b]pyridin-6-yl
- 25 3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]thiazin-6-yl
- 7-chloro-3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]thiazin-6-yl
- 7-fluoro-3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]thiazin-6-yl
- 2-oxo-2,3-dihydro-1H-pyrido[3,4-b][1,4]thiazin-7-yl
- 30 especially:
- 4H-benzo[1,4]thiazin-3-one-6-yl (3-oxo-3,4-dihydro-2H-benzo[1,4]thiazin-6-yl)
- benzo[1,3]dioxol-5-yl
- 2,3-Dihydro-benzo[1,4]dioxin-6-yl
- 4-fluorobenzimidazol-2-yl
- 35 benzo[1,2,5]thiadiazol-5-yl
- quinoxalin-2-yl
- 2-oxo-2,3-dihydro-1H-pyrido[2,3-b][1,4]thiazin-7-yl
- 2,3-dihydro-[1,4]dioxino[2,3-c]pyridin-7-yl.

When used herein, the term "alkyl" includes groups having straight and branched chains, for instance, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, t-butyl, pentyl and hexyl. The term 'alkenyl' should be interpreted accordingly.

5 Halo or halogen includes fluoro, chloro, bromo and iodo.

Haloalkyl moieties include 1-3 halogen atoms.

Unless otherwise defined, the term 'heterocyclic' as used herein includes aromatic and non-aromatic, single and fused, rings suitably containing up to four hetero-atoms in each ring selected from oxygen, nitrogen and sulphur, which rings may be unsubstituted or C-substituted by, for example, up to three groups selected from (C₁₋₄)alkylthio; halo; 10 carboxy(C₁₋₄)alkyl; halo(C₁₋₄)alkoxy; halo(C₁₋₄)alkyl; (C₁₋₄)alkyl; (C₂₋₄)alkenyl; (C₁₋₄)alkoxycarbonyl; formyl; (C₁₋₄)alkylcarbonyl; (C₂₋₄)alkenyloxycarbonyl; (C₂₋₄)alkenylcarbonyl; (C₁₋₄)alkylcarbonyloxy; (C₁₋₄)alkoxycarbonyl(C₁₋₄)alkyl; hydroxy; hydroxy(C₁₋₄)alkyl; mercapto(C₁₋₄)alkyl; (C₁₋₄)alkoxy; nitro; cyano; carboxy; amino or 15 aminocarbonyl optionally substituted as for corresponding substituents in R³; (C₁₋₄)alkylsulphonyl; (C₂₋₄)alkenylsulphonyl; or aminosulphonyl wherein the amino group is optionally substituted by (C₁₋₄)alkyl or (C₂₋₄)alkenyl; optionally substituted aryl, aryl(C₁₋₄)alkyl or aryl(C₁₋₄)alkoxy and oxo groups. Each heterocyclic ring suitably has from 4 to 7, preferably 5 or 6, ring atoms. A fused heterocyclic ring system may include 20 carbocyclic rings and need include only one heterocyclic ring. Compounds within the invention containing a heterocyclyl group may occur in two or more tautomeric forms depending on the nature of the heterocyclyl group; all such tautomeric forms are included within the scope of the invention.

Where an amino group forms part of a single or fused non-aromatic heterocyclic 25 ring as defined above suitable optional substituents in such substituted amino groups include H; trifluoromethyl; (C₁₋₄)alkyl optionally substituted by hydroxy, (C₁₋₆)alkoxy, (C₁₋₆)alkylthio, halo or trifluoromethyl; (C₂₋₄)alkenyl; aryl; aryl (C₁₋₄)alkyl; (C₁₋₄)alkoxycarbonyl; (C₁₋₄)alkylcarbonyl; formyl; (C₁₋₆)alkylsulphonyl; or aminocarbonyl wherein the amino group is optionally substituted by (C₁₋₄)alkoxycarbonyl, (C₁₋₄)alkylcarbonyl, (C₂₋₄)alkenyloxycarbonyl, (C₂₋₄)alkenylcarbonyl, (C₁₋₄)alkyl or (C₂₋₄)alkenyl and optionally further substituted by (C₁₋₄)alkyl or (C₂₋₄)alkenyl. 30

When used herein the term 'aryl', includes phenyl and naphthyl, each optionally substituted with up to five, preferably up to three, groups selected from (C₁₋₄)alkylthio; halo; carboxy(C₁₋₄)alkyl; halo(C₁₋₄)alkoxy; halo(C₁₋₄)alkyl; (C₁₋₄)alkyl; (C₂₋₄)alkenyl; (C₁₋₄)alkoxycarbonyl; formyl; (C₁₋₄)alkylcarbonyl; (C₂₋₄)alkenyloxycarbonyl; (C₂₋₄)alkenylcarbonyl; (C₁₋₄)alkylcarbonyloxy; (C₁₋₄)alkoxycarbonyl(C₁₋₄)alkyl; hydroxy; hydroxy(C₁₋₄)alkyl; mercapto(C₁₋₄)alkyl; (C₁₋₄)alkyl; 35

4)alkoxy; nitro; cyano, carboxy; amino or aminocarbonyl optionally substituted as for corresponding substituents in R³; (C₁₋₄)alkylsulphonyl; (C₂₋₄)alkenylsulphonyl; or aminosulphonyl wherein the amino group is optionally substituted by (C₁₋₄)alkyl or (C₂₋₄)alkenyl; phenyl, phenyl(C₁₋₄)alkyl or phenyl(C₁₋₄)alkoxy.

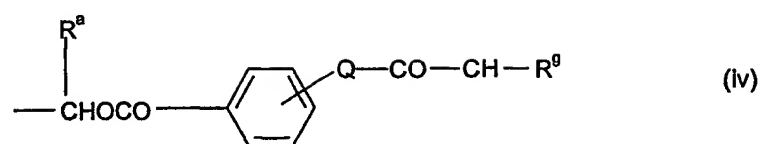
- 5 The term 'acyl' includes (C₁₋₆)alkoxycarbonyl, formyl or (C₁₋₆) alkylcarbonyl groups.

Some of the compounds of this invention may be crystallised or recrystallised from solvents such as aqueous and organic solvents. In such cases solvates may be formed. This invention includes within its scope stoichiometric solvates including
10 hydrates as well as compounds containing variable amounts of water that may be produced by processes such as lyophilisation.

Since the compounds of formula (I) are intended for use in pharmaceutical compositions it will readily be understood that they are each provided in substantially pure form, for example at least 60% pure, more suitably at least 75% pure and preferably
15 at least 85%, especially at least 98% pure (% are on a weight for weight basis). Impure preparations of the compounds may be used for preparing the more pure forms used in the pharmaceutical compositions; these less pure preparations of the compounds should contain at least 1%, more suitably at least 5% and preferably from 10 to 59% of a
20 compound of the formula (I) or pharmaceutically acceptable derivative thereof.

Pharmaceutically acceptable derivatives of the above-mentioned compounds of formula (I) include the free base form or their acid addition or quaternary ammonium salts, for example their salts with mineral acids e.g. hydrochloric, hydrobromic, sulphuric nitric or phosphoric acids, or organic acids, e.g. acetic, fumaric, succinic, maleic, citric, benzoic, p-toluenesulphonic, methanesulphonic, naphthalenesulphonic acid or tartaric
25 acids. Compounds of formula (I) may also be prepared as the N-oxide. Compounds of formula (I) having a free carboxy group may also be prepared as an *in vivo* hydrolysable ester. The invention extends to all such derivatives.

Examples of suitable pharmaceutically acceptable *in vivo* hydrolysable ester-forming groups include those forming esters which break down readily in the human
30 body to leave the parent acid or its salt. Suitable groups of this type include those of part formulae (i), (ii), (iii), (iv) and (v):

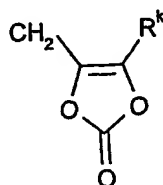


- 5 wherein R^a is hydrogen, (C₁₋₆) alkyl, (C₃₋₇) cycloalkyl, methyl, or phenyl, R^b is (C₁₋₆) alkyl, (C₁₋₆) alkoxy, phenyl, benzyl, (C₃₋₇) cycloalkyl, (C₃₋₇) cycloalkyloxy, (C₁₋₆) alkyl (C₃₋₇) cycloalkyl, 1-amino (C₁₋₆) alkyl, or 1-(C₁₋₆ alkyl)amino (C₁₋₆) alkyl; or R^a and R^b together form a 1,2-phenylene group optionally substituted by one or
- 10 two methoxy groups; R^c represents (C₁₋₆) alkylene optionally substituted with a methyl or ethyl group and R^d and R^e independently represent (C₁₋₆) alkyl; R^f represents (C₁₋₆) alkyl; R^g represents hydrogen or phenyl optionally substituted by up to three groups selected from halogen, (C₁₋₆) alkyl, or (C₁₋₆) alkoxy; Q is oxygen or NH; R^h is hydrogen or (C₁₋₆) alkyl; Rⁱ is hydrogen, (C₁₋₆) alkyl optionally substituted by halogen,
- 15 (C₂₋₆) alkenyl, (C₁₋₆) alkoxycarbonyl, aryl or heteroaryl; or R^h and Rⁱ together form (C₁₋₆) alkylene; R^j represents hydrogen, (C₁₋₆) alkyl or (C₁₋₆) alkoxycarbonyl; and R^k represents (C₁₋₈) alkyl, (C₁₋₈) alkoxy, (C₁₋₆) alkoxy(C₁₋₆)alkoxy or aryl.

- Examples of suitable *in vivo* hydrolysable ester groups include, for example, acyloxy(C₁₋₆)alkyl groups such as acetoxymethyl, pivaloyloxymethyl, α-acetoxyethyl,
- 20 α-pivaloyloxyethyl, 1-(cyclohexylcarbonyloxy)prop-1-yl, and (1-aminoethyl)carbonyloxymethyl; (C₁₋₆)alkoxycarbonyloxy(C₁₋₆)alkyl groups, such as ethoxycarbonyloxymethyl, α-ethoxycarbonyloxyethyl and propoxycarbonyloxyethyl; di(C₁₋₆)alkylamino(C₁₋₆)alkyl especially di(C₁₋₄)alkylamino(C₁₋₄)alkyl groups such as

dimethylaminomethyl, dimethylaminoethyl, diethylaminomethyl or diethylaminoethyl;
 2-((C₁₋₆)alkoxycarbonyl)-2-(C₂₋₆)alkenyl groups such as
 2-(isobutoxycarbonyl)pent-2-enyl and 2-(ethoxycarbonyl)but-2-enyl; lactone groups such
 as phthalidyl and dimethoxyphthalidyl.

- 5 A further suitable pharmaceutically acceptable *in vivo* hydrolysable ester-forming
 group is that of the formula:

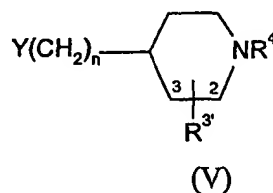
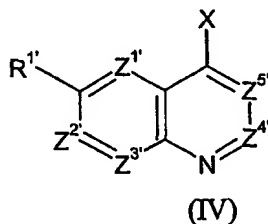


wherein R^k is hydrogen, C₁₋₆ alkyl or phenyl.

- 10 R is preferably hydrogen.

Certain of the above-mentioned compounds of formula (I) may exist in the form
 of optical isomers, e.g. diastereoisomers and mixtures of isomers in all ratios, e.g. racemic
 mixtures. The invention includes all such forms, in particular the pure isomeric forms.
 For examples the invention includes compound in which an A-B group CH(OH)-CH₂ is
 15 in either isomeric configuration the *R*-isomer is preferred. The different isomeric forms
 may be separated or resolved one from the other by conventional methods, or any given
 isomer may be obtained by conventional synthetic methods or by stereospecific or
 asymmetric syntheses..

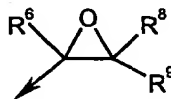
- In a further aspect of the invention there is provided a process for preparing
 20 compounds of formula (I), or a pharmaceutically acceptable derivative thereof, which
 process comprises reacting a compound of formula (IV) with a compound of formula (V):



- 25 wherein n is as defined in formula (I); Z^{1'}, Z^{2'}, Z^{3'}, Z^{4'}, Z^{5'}, R^{1'}, R^{3'} and R^{4'} are Z¹, Z²,
 Z³, Z⁴, Z⁵, R¹, R³ and R⁴ as defined in formula (I) or groups convertible thereto;
 and X and Y may be the following combinations:

- (i) one of X and Y is CO₂R^Y and the other is CH₂CO₂R^X;
 30 (ii) X is CHR⁶R⁷ and Y is C(=O)R⁹;
 (iii) X is CR⁷=PR^Z₃ and Y is C(=O)R⁹;

- (iv) X is $C(=O)R^7$ and Y is $CR^9=PR^Z_3$;
 - (v) one of Y and X is COW and the other is $NHR^{11'}$, NCO or $NR^{11'}COW$;
 - (vi) X is $NHR^{11'}$ and Y is $C(=O)R^8$ or X is $C(=O)R^6$ and Y is $NHR^{11'}$;
 - (vii) X is $NHR^{11'}$ and Y is CR^8R^9W ;
 - 5 (viii) X is W or OH and Y is CH_2OH ;
 - (ix) X is $NHR^{11'}$ and Y is SO_2W ;
 - (x) one of X and Y is $(CH_2)_p-W$ and the other is $(CH_2)_qNHR^{11'}$, $(CH_2)_qOH$, $(CH_2)_qSH$ or $(CH_2)_qSCOR^X$ where $p+q=1$;
 - (xi) one of X and Y is OH and the other is $-CH=N_2$;
 - 10 (xii) X is NCO and Y is OH or NH_2 ;
 - (xiii) X is $CR^6R^7SO_2W$, $A'COW$, $CR^6=CH_2$ or oxirane and Y is $NHR^{11'}$;
 - (xiv) X is W and Y is $CONHR^{11'}$ or $OCONH_2$;
- in which W is a leaving group, e.g. halo, methanesulphonyloxy, trifluoromethanesulphonyloxy or imidazolyl; R^X and R^Y are $(C_{1-6})alkyl$; R^Z is aryl or $(C_{1-6})alkyl$; A' and $NR^{11'}$ are A and NR^{11} as defined in formula (I), or groups convertible thereto; and oxirane is:



- wherein R^6 , R^8 and R^9 are as defined in formula (I);
- 20 and thereafter optionally or as necessary converting A' , Z^1 , Z^2 , Z^3 , Z^4 , Z^5 , R^1 , R^3 , R^4 and $NR^{11'}$ to A, Z^1 , Z^2 , Z^3 , Z^4 , Z^5 , R^1 , R^3 , R^4 and $NR^{11'}$; converting A-B to other A-B, interconverting R^1 , R^3 and/or R^4 , and/or forming a pharmaceutically acceptable derivative thereof.

- Process variant (i) initially produces compounds of formula (I) wherein A-B is
- 25 $CO-CH_2$ or CH_2-CO .

Process variant (ii) initially produces compounds of formula (I) wherein A-B is $CR^6R^7-CR^9OH$.

Process variant (iii) and (iv) initially produce compounds of formula (I) wherein A-B is $CR^7=CR^9$.

- 30 Process variant (v) initially produces compounds of formula (I) where A-B is $CO-NR^{11}$ or $NR^{11}-CO$.

Process variant (vi) initially produces compounds of formula (I) wherein A-B is $NR^{11}-CHR^8$ or CHR^6-NHR^{11} .

- 35 Process variant (vii) initially produces compounds of formula (I) wherein A-B is $NR^{11'}-CR^8R^9$.

Process variant (viii) initially produces compounds of formula (I) wherein A-B is O-CH₂.

Process variant (ix) initially produces compounds where AB is NR¹¹SO₂.

Process variant (x) initially produces compounds of formula (I) wherein one of A
5 and B is CH₂ and the other is NHR¹¹, O or S.

Process variant (xi) initially produces compounds of formula a(I) wherein A-B is OCH₂ or CH₂O.

Process variant (xii) initially produces compounds where AB is NH-CO-NH or NH-CO-O.

10 Process variant (xiii) initially produces compounds where n is 0 and AB is CR⁶R⁷SO₂NR¹¹, A'-CONR¹¹ or CR⁶R⁷CR⁸R⁹NR¹¹.

Process variant (xiv) produces compounds where AB is NR¹¹CO or NH-CO-O.

In process variants (v) and (xiii) (second variant) the reaction is a standard amide or urea formation reaction involving e.g.:

- 15 1. Activation of a carboxylic acid (e.g. to an acid chloride, mixed anhydride, active ester, O-acyl-isourea or other species), and treatment with an amine (Ogliaruso, M.A.; Wolfe, J.F. in *The Chemistry of Functional Groups (Ed. Patai, S.) Suppl. B: The Chemistry of Acid Derivatives, Pt. 1* (John Wiley and Sons, 1979), pp 442-8; Beckwith, A.L.J. in *The Chemistry of Functional Groups (Ed. Patai, S.) Suppl. B: The Chemistry of Amides (Ed. Zabricky, J.)* (John Wiley and Sons, 1970), p 73 ff. The acid and amine are preferably
20 reacted in the presence of an activating agent such as 1-(dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) or 1-hydroxybenzotriazole (HOBT) or O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU); or
2. The specific methods of:
25 a. *in situ* conversion of an acid into the amine component by a modified Curtius reaction procedure (Shioiri, T., Murata, M., Hamada, Y., *Chem. Pharm. Bull.* 1987, 35, 2698)
b. *in situ* conversion of the acid component into the acid chloride under neutral conditions (Villeneuve, G. B.; Chan, T. H., *Tetrahedron. Lett.* 1997, 38, 6489).

A' may be, for example, protected hydroxymethylene.

30 The process variant (xiii) (third variant) is a standard addition reaction using methods well known to those skilled in the art. The process is preferably carried out in a polar organic solvent e.g. acetonitrile in the presence of an organic base e.g. triethylamine.

In process variant (xiii) (fourth variant) the coupling may be effected in
35 acetonitrile at room temperature in the presence of one equivalent of lithium perchlorate as catalyst (general method of J.E. Chateaneuf *et al*, *J. Org. Chem.*, 56, 5939-5942, 1991) or more preferably with ytterbium triflate in dichloromethane. In some cases an

elevated temperature such as 40 – 70 °C may be beneficial. Alternatively, the piperidine may be treated with a base, such as one equivalent of butyl lithium, and the resulting salt reacted with the oxirane in an inert solvent such as tetrahydrofuran, preferably at an elevated temperature such as 80°C. Use of a chiral epoxide will afford single
5 diastereomers. Alternatively, mixtures of diastereomers may be separated by preparative HPLC or by conventional resolution through crystallisation of salts formed from chiral acids.

The process variant (xii) is a standard urea or carbamate formation reactions from the reaction of an isocyanate with an amine or alcohol and is conducted by methods well
10 known to those skilled in the art (for example see March, J; *Advanced Organic Chemistry, Edition 3* (John Wiley and Sons, 1985), p802-3). The process is preferably carried out in a polar solvent such as N,N-dimethylformamide.

In process variant (i) the process is two step: firstly a condensation using a base, preferably sodium hydride or alkoxide, sodamide, alkyl lithium or lithium dialkylamide, preferably in an aprotic solvent e.g. ether, THF or benzene; secondly, hydrolysis using an
15 inorganic acid, preferably HCl in aqueous organic solvent at 0-100°C. Analogous routes are described in DE330945, EP31753, EP53964 and H. Sargent, J. Am. Chem. Soc. 68, 2688-2692 (1946). Similar Claisen methodology is described in Soszko et. al., Pr.Kom.Mat. Przyr.Poznan.Tow.Przyj.Nauk., (1962), 10, 15.

In process variant (ii) the reaction is carried out in the presence of a base, preferably organometallic or metal hydride e.g. NaH, lithium diisopropylamide or NaOEt, preferably in an aprotic solvent, preferably THF, ether or benzene at -78 to 25°C
20 (analogous process in Gutswiller et al. (1978) J. Am. Chem. Soc. 100, 576).

In process variants (iii) and (iv) if a base is used it is preferably NaH, KH, an alkyl
25 lithium e.g. BuLi, a metal alkoxide e.g. NaOEt, sodamide or lithium dialkylamide e.g. diisopropylamide. An analogous method is described in US 3989691 and M.Gates et. al. (1970) J. Amer.Chem.Soc., 92, 205, as well as Taylor et al. (1972) JACS 94, 6218.

In process variant (vi) the reaction is a standard reductive alkylation using, e.g., sodium borohydride or sodium triacetoxyborohydride (Gribble, G. W. in *Encyclopedia of Reagents for Organic Synthesis* (Ed. Paquette, L. A.) (John Wiley and Sons, 1995), p
30 4649).

The process variant (vii) is a standard alkylation reaction well known to those skilled in the art, for example where an alcohol or amine is treated with an alkyl halide in the presence of a base (for example see March, J; *Advanced Organic Chemistry, Edition 3*
35 (John Wiley and Sons, 1985), p364-366 and p342-343). The process is preferably carried out in a polar solvent such as N,N-dimethylformamide

In process variant (xiii) (first variant) the reaction is a standard sulphonamide formation reaction well known to those skilled in the art. This may be e.g. the reaction of a sulphonyl halide with an amine.

In process variant (viii) where X is W such as halogen, methanesulphonyloxy or trifluoromethanesulphonyloxy, the hydroxy group in Y is preferably converted to an OM group where M is an alkali metal by treatment of an alcohol with a base. The base is preferably inorganic such as NaH, lithium diisopropylamide or sodium. Where X is OH, the hydroxy group in Y is activated under Mitsunobu conditions (Fletcher et.al. J Chem Soc. (1995), 623). Alternatively the X=O and Y=CH₂OH groups can be reacted directly by activation with 1,3-dicyclohexylcarbodiimide (DCC) (Chem. Berichte 1962, 95, 2997 or Angewante Chemie 1963 75, 377).

In process variant (ix) the reaction is conducted in the presence of an organic base such as triethylamine or pyridine such as described by Fuhrman et.al., J. Amer. Chem. Soc.; 67, 1245, 1945. The X=NR¹¹SO₂W or Y=SO₂W intermediates can be formed from the requisite amine e.g. by reaction with SO₂Cl₂ analogously to the procedure described by the same authors Fuhrman et.al., J. Amer. Chem. Soc.; 67, 1245, 1945.

In process variant (x) where one of X and Y contains NHR¹¹ the leaving group W is halogen and the reaction is a standard amine formation reaction such as direct alkylation described in (Malpass, J. R., in *Comprehensive Organic Chemistry*, Vol. 2 (Ed. Sutherland, I. O.), p 4 ff.) or aromatic nucleophilic displacement reactions (see references cited in *Comprehensive Organic Chemistry*, Vol. 6, p 946-947 (reaction index); Smith, D. M. in *Comprehensive Organic Chemistry*, Vol. 4 (Ed. Sammes, P. G.) p 20 ff.). This is analogous to the methods described in GB 1177849.

In process variant (x) where one of X and Y contains OH or SH, this is preferably converted to an OM or SM group where M is an alkali metal by treatment of an alcohol, thiol or thioacetate with a base. The base is preferably inorganic such as NaH, lithium diisopropylamide or sodium, or, for SH, metal alkoxide such as sodium methoxide. The X/Y group containing the thioacetate SCOR^x is prepared by treatment of an alcohol or alkyl halide with thioacetic acid or a salt thereof under Mitsunobu conditions. The leaving group V is a halogen. The reaction may be carried out as described in Chapman et.al., J. Chem Soc., (1956), 1563, Gilligan et. al., J. Med. Chem., (1992), 35, 4344, Aloup et. al., J. Med. Chem. (1987), 30, 24, Gilman et al., J.A.C.S. (1949), 71, 3667 and Clinton et al., J.A.C.S. (1948), 70, 491, Barluenga et al., J. Org. Chem. (1987) 52, 5190. Alternatively where X is OH and Y is CH₂V, V is a hydroxy group activated under Mitsunobu conditions (Fletcher et.al. J Chem Soc. (1995), 623).

In process variant (xi) the reaction is as described in den Hertog et. al., *recl.Trav. Chim. Pays-Bas*, (1950), 69, 700.

In process variant (xiv) the leaving group W is preferably chloro, bromo or trifluoromethylsulphonyl and the reaction is the palladium catalysed process known as the "Buchwald" reaction (J. Yin and S. L. Buchwald, *Org.Lett.*, 2000, 2, 1101).

Reduction of a carbonyl group A or B to CHOH can be readily accomplished using reducing agents well known to those skilled in the art, e.g. sodium borohydride in aqueous ethanol or lithium aluminium hydride in ethereal solution. This is analogous to methods described in EP53964, US384556 and J. Gutzwiller *et al*, *J. Amer. Chem. Soc.*, 1978, 100, 576.

The carbonyl group A or B may be reduced to CH₂ by treatment with a reducing agent such as hydrazine in ethylene glycol, at e.g. 130-160°C, in the presence of potassium hydroxide.

Reaction of a carbonyl group A or B with an organometallic reagent yields a group where R⁶ or R⁸ is OH and R⁷ or R⁹ is alkyl.

A hydroxy group on A or B may be oxidised to a carbonyl group by oxidants well known to those skilled in the art, for example, manganese dioxide, pyridinium chlorochromate or pyridinium dichromate.

A hydroxyalkyl A-B group CHR⁷CR⁹OH or CR⁷(OH)CHR⁹ may be dehydrated to give the group CR⁷=CR⁹ by treatment with an acid anhydride such as acetic anhydride.

Methods for conversion of CR⁷=CR⁹ by reduction to CHR⁷CHR⁹ are well known to those skilled in the art, for example using hydrogenation over palladium on carbon as catalyst. Methods for conversion of CR⁷=CR⁹ to give the A-B group CR⁷(OH)CHR⁹ or CHR⁷CR⁹OH are well known to those skilled in the art for example by epoxidation and subsequent reduction by metal hydrides, hydration, hydroboration or oxymercuration.

An amide carbonyl group may be reduced to the corresponding amine using a reducing agent such as lithium aluminium hydride.

A hydroxy group in A or B may be converted to azido by activation and displacement e.g. under Mitsunobu conditions using hydrazoic acid or by treatment with diphenylphosphorylazide and base, and the azido group in turn may be reduced to amino by hydrogenation.

Examples of groups Z^{1'}, Z^{2'}, Z^{3'}, Z^{4'}, Z^{5'}, are CR^{1a'} where R^{1a'} is a group convertible to R^{1a}. Z^{1'}, Z^{2'}, Z^{3'}, Z^{4'} and Z^{5'} are preferably Z¹, Z², Z³, Z⁴ and Z⁵.

R^{1a'} and R^{1'} are preferably R^{1a} and R¹. R^{1'} is preferably methoxy. R^{3'} is R³ or more preferably hydrogen, vinyl, alkoxycarbonyl or carboxy. R^{4'} is R⁴ or more

preferably H or an N-protecting group such as t-butoxycarbonyl, benzyloxycarbonyl or 9-fluorenylmethyloxycarbonyl.

Conversions of R^{1a} , R^1 , $R^{3'}$ and $R^{4'}$ and interconversions of R^{1a} , R^1 , R^3 and R^4 are conventional. In compounds which contain an optionally substituted hydroxy group, suitable conventional hydroxy protecting groups which may be removed without disrupting the remainder of the molecule include acyl and alkylsilyl groups. N protecting groups are removed by conventional methods.

For example R^1 methoxy is convertible to R^1 hydroxy by treatment with lithium and diphenylphosphine (general method described in Ireland et. al. (1973) J.Amer.Chem.Soc., 7829) or HBr. Alkylation of the hydroxy group with a suitable alkyl derivative bearing a leaving group such as halide and a protected amino, piperidyl, amidino or guanidino group or group convertible thereto, yields, after conversion/deprotection, R^1 alkoxy substituted by optionally N-substituted amino, piperidyl, guanidino or amidino.

R^3 alkenyl is convertible to hydroxyalkyl by hydroboration using a suitable reagent such as 9-borabicyclo[3.3.1]nonane, epoxidation and reduction or oxymercuration.

R^3 1,2-dihydroxy can be prepared from $R^{3'}$ alkenyl using osmium tetroxide or other reagents well known to those skilled in the art (see Advanced Organic Chemistry (Ed. March, J.) (John Wiley and Sons, 1985), p 732-737 and refs. cited therein) or epoxidation followed by hydrolysis (see Advanced Organic Chemistry (Ed. March, J.) (John Wiley and Sons, 1985), p 332,333 and refs. cited therein).

R^3 vinyl can be chain extended by standard homologation e.g by conversion to hydroxyethyl followed by oxidation to the aldehyde which is then subjected to a Wittig reaction.

Opening an epoxide $R^{3'}$ group with cyanide anion yields a $CH(OH)-CH_2CN$ group.

Opening an epoxide-containing $R^{3'}$ group with azide anion yields an azide derivative which can be reduced to the amine. Conversion of the amine to a carbamate is followed by ring closure with base to give the 2-oxo-oxazolidinyl containing R^3 group.

Substituents on R^3 alkyl or alkenyl may be interconverted by conventional methods, for example hydroxy may be derivatised by esterification, acylation or etherification. Hydroxy groups may be converted to halogen, thiol, alkylthio, azido, alkylcarbonyl, amino, aminocarbonyl, oxo, alkylsulphonyl, alkenylsulphonyl or aminosulphonyl by conversion to a leaving group and substitution by the required group, hydrolysis or oxidation as appropriate or reaction with an activated acid, isocyanate or alkoxyisocyanate. Primary and secondary hydroxy groups can be oxidised to an aldehyde

or ketone respectively and alkylated with a suitable agent such as an organometallic reagent to give a secondary or tertiary alcohol as appropriate. A carboxylate group may be converted to an hydroxymethyl group by reduction of an ester of this acid with a suitable reducing agent such as lithium aluminium hydride.

5 Substituted 2-oxo-oxazolidinyl containing R^3 groups may be prepared from the corresponding aldehyde by conventional reaction with a glycine anion equivalent, followed by cyclisation of the resulting amino alcohol (M Grauert *et al*, *Ann Chem* (1985) 1817, Rozenberg *et al*, *Angew Chem Int Ed Engl* (1994) 33(1) 91). The resulting 2-oxo-oxazolidinyl group contains a carboxy group which can be converted to other R^{10} groups
10 by standard procedures.

Carboxy groups within R^3 may be prepared by Jones' oxidation of the corresponding alcohols CH_2OH using chromic acid and sulphuric acid in water/methanol (E.R.H. Jones *et al*, *J.C.S.* 1946,39). Other oxidising agents may be used for this transformation such as sodium periodate catalysed by ruthenium trichloride (G.F.Tutwiler
15 *et al*, *J.Med.Chem.*, 1987, 30(6), 1094), chromium trioxide-pyridine (G. Just *et al*, *Synth. Commun.* 1979, 9(7), 613), potassium permanganate (D.E.Reedich *et al*, *J. Org. Chem.*,1985,50(19),3535, and pyridinium chlorochromate (D. Askin *et al*, *Tetrahedron Letters*, 1988, 29(3), 277).

The carboxy group may alternatively be formed in a two stage process, with an
20 initial oxidation of the alcohol to the corresponding aldehyde using for instance dimethyl sulphoxide activated with oxalyl chloride (N.Cohen *et al*, *J. Am. Chem. Soc.*, 1983, 105, 3661) or dicyclohexylcarbodiimide (R.M.Wengler, *Angew. Chim. Int. Ed. Eng.*, 1985, 24(2), 77), or oxidation with tetrapropylammonium perruthenate (Ley *et al*, *J. Chem.Soc. Chem Commun.*,1987, 1625). The aldehyde may then be separately oxidised to the
25 corresponding acid using oxidising agents such as silver (II) oxide (R.Grigg *et al*, *J. Chem. Soc. Perkin1*,1983, 1929), potassium permanganate (A.Zurcher, *Helv. Chim. Acta.*, 1987, 70 (7), 1937), sodium periodate catalysed by ruthenium trichloride (T.Sakata *et al*, *Bull. Chem. Soc. Jpn.*, 1988, 61(6), 2025), pyridinium chlorochromate (R.S.Reddy *et al*, *Synth. Commun.*, 1988, 18(51), 545) or chromium trioxide (R.M.Coates *et al*, *J.*
30 *Am. Chem. Soc.*,1982, 104, 2198).

An R^3 CO_2H group may also be prepared from oxidative cleavage of the corresponding diol, $CH(OH)CH_2OH$, using sodium periodate catalysed by ruthenium trichloride with an acetonitrile-carbontetrachloride-water solvent system (V.S.Martin *et al*, *Tetrahedron Letters*, 1988, 29(22), 2701).

35 R^3 groups containing a cyano or carboxy group may also be prepared by conversion of an alcohol to a suitable leaving group such as the corresponding tosylate by reaction with para-toluenesulphonyl chloride (M.R.Bell, *J. Med. Chem.*,1970, 13, 389), or

the iodide using triphenylphosphine, iodine, and imidazole (G. Lange, *Synth. Commun.*, 1990, 20, 1473). The second stage is the displacement of the leaving group with cyanide anion (L.A. Paquette et al, *J. Org. Chem.*, 1979, 44 (25), 4603; P.A. Grieco et al, *J. Org. Chem.*, 1988, 53 (16), 3658). Finally acidic hydrolysis of the nitrile group gives the
5 desired acids (H. Rosemeyer et al, *Heterocycles*, 1985, 23 (10), 2669). The hydrolysis may also be carried out with base e.g. potassium hydroxide (H. Rapoport, *J. Org. Chem.*, 1958, 23, 248) or enzymatically (T. Beard et al, *Tetrahedron Asymmetry*, 1993, 4 (6), 1085).

Other functional groups in R^3 may be obtained by conventional conversions of carboxy or cyano groups.

10 Tetrazoles are conveniently prepared by reaction of sodium azide with the cyano group (e.g. F. Thomas et al, *Bioorg. Med. Chem. Lett.*, 1996, 6 (6), 631; K. Kubo et al, *J. Med. Chem.*, 1993, 36, 2182) or by reaction of azidotri-*n*-butyl stannane with the cyano group followed by acidic hydrolysis (P.L. Ornstein, *J. Org. Chem.*, 1994, 59, 7682 and *J. Med. Chem.*, 1996, 39 (11), 2219).

15 The 3-hydroxy-3-cyclobutene-1,2-dione-4-yl group (e.g. R.M. Soll, *Bioorg. Med. Chem. Lett.*, 1993, 3 (4), 757 and W. A. Kinney, *J. Med. Chem.*, 1992, 35 (25), 4720) can be prepared by the following sequence:- (1) a compound where R^3 is $(CH_2)_nCHO$ ($n = 0, 1, 2$) is treated with triethylamine/carbon tetrabromide triphenylphosphine to give initially $(CH_2)_nCH=CBr_2$; (2) dehydrobromination of this intermediate to give the
20 corresponding bromoethyne derivative $(CH_2)_nC\equiv CBr$ (for this 2 stage sequence see D. Grandjean et al, *Tetrahedron Letters*, 1994, 35 (21), 3529); (3) palladium-catalysed coupling of the bromoethyne with 4-(1-methylethoxy)-3-(tri-*n*-butylstannyl)cyclobut-3-ene-1,2-dione (Liebeskind et al, *J. Org. Chem.*, 1990, 55, 5359); (4) reduction of the ethyne moiety to $-CH_2CH_2-$ under standard conditions of hydrogen and palladium on charcoal catalysis (see Howard et al, *Tetrahedron*, 1980, 36, 171); and finally (4) acidic
25 hydrolysis of the methylethoxyester to generate the corresponding 3-hydroxy-3-cyclobutene-1,2-dione group (R.M. Soll, *Bioorg. Med. Chem. Lett.*, 1993, 3 (4), 757).

The tetrazol-5-ylaminocarbonyl group may be prepared from the corresponding carboxylic acid and 2-aminotetrazole by dehydration with standard peptide coupling
30 agents such as 1,1'-carbonyldiimidazole (P. L. Ornstein et al, *J. Med. Chem.*, 1996, 39 (11), 2232).

The alkyl- and alkenyl-sulphonylcarboxamides are similarly prepared from the corresponding carboxylic acid and the alkyl- or alkenyl-sulphonamide by dehydration with standard peptide coupling agents such as 1,1'-carbonyldiimidazole (P. L. Ornstein et al, *J. Med. Chem.*, 1996, 39 (11), 2232).
35

The hydroxamic acid groups are prepared from the corresponding acids by standard amide coupling reactions eg N. R. Patel et al, *Tetrahedron*, 1987, 43 (22), 5375

2,4-thiazolidinedione groups may prepared from the aldehydes by condensation with 2,4-thiazolidinedione and subsequent removal of the olefinic double bond by hydrogenation.

The preparation of 5-oxo-1,2,4-oxadiazoles from nitriles is described by
 5 Y.Kohara et al, Bioorg. Med. Chem. Lett., 1995, 5(17), 1903.

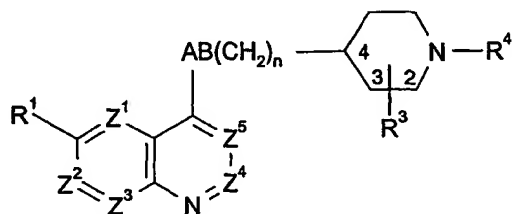
1,2,4-triazol-5-yl groups may be prepared from the corresponding nitrile by reaction with an alcohol under acid conditions followed by reaction with hydrazine and then an R¹⁰-substituted activated carboxylic acid (see JB Polya in 'Comprehensive Heterocyclic Chemistry' Edition 1 p762, Ed AR Katritzky and CW Rees, Pergamon Press,
 10 Oxford 1984 and J.J. Ares et al, J. Heterocyclic Chem., 1991, 28(5), 1197).

NH is converted to NR⁴ by conventional means such as amide or sulphonamide formation with an acyl derivative R⁵V'CO₂W or R⁵V'SO₂W, for compounds where U is CO or SO₂ or, where U is CH₂, by alkylation with an alkyl halide R⁵-V'-CH₂-halide or alkyl derivative R⁵-V'-CH₂-W in the presence of base, acylation/reduction or reductive
 15 alkylation with an aldehyde R⁵-V'-CHO where V' is V or a group convertible thereto such as a dimethyl acetal or 1,3-dithiane.

Where one of R³ and R⁶, R⁷, R⁸ or R⁹ contains a carboxy group and the other contains a hydroxy or amino group they may together form a cyclic ester or amide linkage. This linkage may form spontaneously during coupling of the compound of
 20 formula (IV) and the piperidine moiety or in the presence of standard peptide coupling agents.

It will be appreciated that under certain circumstances interconversions may interfere, for example, hydroxy groups in A or B and the piperidine NH will require protection e.g. as a carboxy- or silyl-ester group for hydroxy and as an acyl derivative for
 25 piperidine nitrogen, during conversion of R^{1a'}, R^{1'}, R^{3'} or R^{4'}, or during the coupling of the compounds of formulae (IV) and (V).

Other routes to compounds of formula (I) include those via the intermediate of formula (VI):



30

prepared by the routes described in WO99/37636, WO00/21948 and WO00/43383.

Compounds of formulae (IV) and (V) are known compounds, (see for example Smith *et al*, *J. Amer. Chem. Soc.*, 1946, 68, 1301) or prepared analogously, see for example the references cited above.

Compounds of formula (IV) where X is $CR^6R^7SO_2W$ may be prepared by a route analogous to that of Ahmed El Hadri *et al*, *J. Heterocyclic Chem.*, 1993, 30(3), 631. Thus compounds of formula (IV) where X is CH_2SO_2OH may be prepared by reacting the corresponding 4-methyl compound with N-bromosuccinimide, followed by treatment with sodium sulfite. The leaving group W may be converted to another leaving group W, e.g. a halogen group, by conventional methods.

The isocyanate of formula (IV) may be prepared conventionally from a 4-amino derivative such as 4-amino-quinoline, and phosgene, or phosgene equivalent (eg triphosgene) or it may be prepared more conveniently from a 4-carboxylic acid by a "one-pot" Curtius Reaction with diphenyl phosphoryl azide (DPPA) [see T. Shiori *et al*. *Chem. Pharm. Bull.* 35, 2698-2704 (1987)].

The 4-amino derivatives are commercially available or may be prepared by conventional procedures from a corresponding 4-chloro derivative by treatment with ammonia (O.G. Backeberg *et al.*, *J. Chem Soc.*, 381, 1942) or propylamine hydrochloride (R. Radinov *et al.*, *Synthesis*, 886, 1986).

4-Alkenyl compounds of formula (IV) may be prepared by conventional procedures from a corresponding 4-halogeno-derivative by e.g. a Heck synthesis as described in e.g. *Organic Reactions*, 1982, 27, 345.

4-Halogeno derivatives of compounds of formula (IV) are commercially available, or may be prepared by methods known to those skilled in the art. A 4-chloroquinoline is prepared from the corresponding quinolin-4-one by reaction with phosphorus oxychloride ($POCl_3$) or phosphorus pentachloride, PCl_5 . A 4-bromo-substituent may be prepared from the quinolin- or naphthyridin-4-one by reaction with phosphorus tribromide (PBr_3) in DMF. A 4-chloroquinazoline is prepared from the corresponding quinazolin-4-one by reaction with phosphorus oxychloride ($POCl_3$) or phosphorus pentachloride, PCl_5 . A quinazolinone and quinazolines may be prepared by standard routes as described by T.A. Williamson in *Heterocyclic Compounds*, 6, 324 (1957) Ed. R.C. Elderfield.

Activated carboxy derivatives $X=A'COW$ of formula (IV) may be prepared from $X=A'CO_2H$ derivatives in turn prepared from CO_2H derivatives by conventional methods such as homologation.

4-Carboxy derivatives of compounds of formula (IV) are commercially available or may be prepared by conventional procedures for preparation of carboxy heteroaromatics well known to those skilled in the art. For example, quinazolines may be prepared by standard routes as described by T.A. Williamson in *Heterocyclic*

Compounds, 6, 324 (1957) Ed. R.C. Elderfield. These 4-carboxy derivatives may be activated by conventional means, e.g. by conversion to an acyl halide or anhydride.

4-Carboxy derivatives such as esters may be reduced to hydroxymethyl derivatives with for example lithium aluminium hydride. Reaction with mesyl chloride and triethylamine would give the mesylate derivative. A diazo compound (X is $-\text{CH}=\text{N}_2$) may be prepared from the 4-carboxaldehyde via the tosyl hydrazone. The 4-carboxaldehyde may be obtained from the same hydroxymethyl derivative by oxidation with standard oxidising agents, eg manganese(II) dioxide.

A 4-oxirane derivative of compounds of formula (IV) is conveniently prepared from the 4-carboxylic acid by first conversion to the acid chloride with oxalyl chloride and then reaction with trimethylsilyldiazomethane to give the diazoketone derivative. Subsequent reaction with 5M hydrochloric acid gives the chloromethylketone. Reduction with sodium borohydride in aqueous methanol gives the chlorohydrin which undergoes ring closure to afford the epoxide on treatment with base, e.g. potassium hydroxide in ethanol-tetrahydrofuran.

Alternatively and preferably, 4-oxirane derivatives can be prepared from bromomethyl ketones which can be obtained from 4-hydroxy compounds by other routes well known to those skilled in the art. For example, hydroxy compounds can be converted to the corresponding 4-trifluoromethanesulphonates by reaction with trifluoromethanesulphonic anhydride under standard conditions (see K. Ritter, *Synthesis*, 1993, 735). Conversion into the corresponding butyloxyvinyl ethers can be achieved by a Heck reaction with butyl vinyl ether under palladium catalysis according to the procedure of W. Cabri *et al*, *J. Org. Chem.*, 1992, **57** (5), 1481. (Alternatively, the equivalent intermediates can be attained by Stille coupling of the trifluoromethanesulphonates or the analogous chloro derivatives with (1-ethoxyvinyl)tributyl tin, (T. R. Kelly, *J. Org. Chem.*, 1996, **61**, 4623.) The alkyloxyvinyl ethers are then converted into the corresponding bromomethylketones by treatment with N-bromosuccinimide in aqueous tetrahydrofuran in a similar manner to the procedures of J. F. W. Keana, *J. Org. Chem.*, 1983, **48**, 3621 and T. R. Kelly, *J. Org. Chem.*, 1996, **61**, 4623.

The 4-hydroxyderivatives can be prepared from an aminoaromatic by reaction with methylpropiolate and subsequent cyclisation, analogous to the method described in N. E. Heindel *et al*, *J. Het. Chem.*, 1969, **6**, 77. For example, 5-amino-2-methoxy pyridine can be converted to 4-hydroxy-6-methoxy-[1,5]naphthyridine using this method.

If a chiral reducing agent such as (+) or (-)-B-chlorodiisopinocampheylborane ['DIP-chloride'] is substituted for sodium borohydride, the prochiral chloromethylketone is converted into the chiral chlorohydrin with ee values generally 85-95% [see C. Bolm *et*

al, Chem. Ber. 125, 1169-1190, (1992)]. Recrystallisation of the chiral epoxide gives material in the mother liquor with enhanced optical purity (typically ee 95%).

The (*R*)-epoxide, when reacted with an amine derivative gives ethanolamine compounds as single diastereomers with (*R*)-stereochemistry at the benzylic position.

5 Alternatively, the epoxide may be prepared from the 4-carboxaldehyde by a Wittig approach using trimethylsulfonium iodide [see G.A. Epling and K-Y Lin, *J. Het. Chem.*, 1987, 24, 853-857], or by epoxidation of a 4-vinyl derivative.

Pyridazines may be prepared by routes analogous to those described in Comprehensive Heterocyclic Chemistry, Volume 3, Ed A.J. Boulton and A. McKillop
10 and naphthyridines may be prepared by routes analogous to those described in Comprehensive Heterocyclic Chemistry, Volume 2, Ed A.J. Boulton and A. McKillop.

4-Hydroxy-1,5-naphthyridines can be prepared from 3-aminopyridine derivatives by reaction with diethyl ethoxymethylene malonate to produce the 4-hydroxy-3-carboxylic acid ester derivative with subsequent hydrolysis to the acid, followed by
15 thermal decarboxylation in quinoline (as for example described for 4-Hydroxy-[1,5]naphthyridine-3-carboxylic acid, J. T. Adams *et al.*, *J. Amer. Chem. Soc.*, 1946, 68, 1317). A 4-hydroxy-[1,5]naphthyridine can be converted to the 4-chloro derivative by heating in phosphorus oxychloride, or to the 4-methanesulphonyloxy or 4-trifluoromethanesulphonyloxy derivative by reaction with methanesulphonyl chloride or
20 trifluoromethanesulphonic anhydride, respectively, in the presence of an organic base. A 4-amino 1,5-naphthyridine can be obtained from the 4-chloro, 4-methanesulphonyloxy or 4-trifluoromethanesulphonyloxy derivative by reaction with n-propylamine in pyridine.

Similarly, 6-methoxy-1,5-naphthyridine derivatives can be prepared from 3-amino-6-methoxypyridine.

25 1,5-Naphthyridines may be prepared by other methods well known to those skilled in the art (for examples see P.A. Lowe in "Comprehensive Heterocyclic Chemistry" Volume 2, p581-627, Ed A.R. Katritzky and C.W. Rees, Pergamon Press, Oxford, 1984).

The 4-hydroxy and 4-amino-cinnolines may be prepared following methods well known to those skilled in the art [see A.R. Osborn and K. Schofield, *J. Chem. Soc.* 2100
30 (1955)]. For example, a 2-aminoacetophenone is diazotised with sodium nitrite and acid to produce the 4-hydroxycinnoline with conversion to chloro and amino derivatives as described for 1,5-naphthyridines.

The substituted piperidines of formula (V) are either commercially available or may be prepared by conventional methods.

35 For compounds of formula (V), where Y is NHR^{11'} suitable amines may be prepared from the corresponding 4-substituted piperidine acid or alcohol. In a first instance, an N-protected piperidine containing an acid bearing substituent, can undergo a

Curtius rearrangement and the intermediate isocyanate can be converted to a carbamate by reaction with an alcohol. Conversion to the amine may be achieved by standard methods well known to those skilled in the art used for amine protecting group removal. For example, an acid substituted N-protected piperidine can undergo a Curtius
5 rearrangement e.g. on treatment with diphenylphosphoryl azide and heating, and the intermediate isocyanate reacts in the presence of 2-trimethylsilylethanol to give the trimethylsilylethylcarbamate (T.L. Capson & C.D. Poulter, *Tetrahedron Lett.*, 1984, 25, 3515). This undergoes cleavage on treatment with tetrabutylammonium fluoride to give the 4-amine substituted N-protected piperidine. Alternatively, an acid group $(\text{CH}_2)_n$ -
10 $^1\text{CO}_2\text{H}$ may be converted to $(\text{CH}_2)_n\text{NHR}^{11}$ by reaction with an activating agent such as isobutyl chloroformate followed by an amine R^{11}NH_2 and the resulting amide reduced with a reducing agent such as LiAlH_4 .

In a second instance, an N-protected piperidine containing an alcohol bearing substituent undergoes a Mitsunobu reaction (for example as reviewed in Mitsunobu,
15 *Synthesis*, (1981), 1), for example with succinimide in the presence of diethyl azodicarboxylate and triphenylphosphine to give the phthalimidoethylpiperidine. Removal of the phthaloyl group, for example by treatment with methylhydrazine, gives the amine of formula (V).

Compounds of formula (V) where $n=1$ may be prepared from the compound
20 where $n=0$ by homologation eg starting from a compound of formula (V) where $\text{Y}=\text{CO}_2\text{H}$.

Compounds of formula (V) with a $-\text{CONHR}^{11}$ group may be prepared from the corresponding nitrile by partial hydrolysis with concentrated mineral acid at ambient temperature, such as concentrated hydrochloric acid (M. Brown *et al*, *J. Med. Chem.*,
25 1999, 42, (9), 1537) or with concentrated sulphuric acid (F. Macias *et al* *Tetrahedron*, 2000, 56, (21), 3409).

Compounds of formula (V) with a $-\text{OCONH}_2$ group may be prepared from the corresponding alcohol by reaction with phosgene followed by ammonia.

Piperidines of formula (V) with substituents in the 2- or 3-positions may generally
30 be prepared from the corresponding 2-, or 3-substituted 4-amino or 4-nitro-pyridine by hydrogenation over a catalyst such as palladium, usually at elevated temperatures and pressures.

Compounds of formula (V) with a R^3 3-hydroxyl group may be prepared from commercially available starting materials such as 1-methyl-1,2,3,6-tetrahydro-pyridine-4-
35 carboxylic acid ethyl ester. This may be demethylated with standard reagents such as 1-chloroethyl chloroformate and N-protected as a suitable carbamate, such as *tert*-butyloxycarbonyl or benzyloxycarbonyl. The olefin may be converted to the

corresponding epoxide with standard agents such as hydrogen peroxide under basic catalysis, or *meta*-chloroperbenzoic acid. The alpha-epoxy ester may be reduced with reagents such as samarium(II) diiodide (see for instance Jones, P.G. *et al*, *Tetrahedron Asymmetry*, 1995, 6 (7),1539) to give the 3-hydroxy-piperidine-4-carboxylic acid derivative. The alcohol can then be protected with for example triethylsilyl or tetrahydropyran-2-yl groups to give a suitably protected intermediate for conversion to compounds of formula (V) with a R³ 3-hydroxyl group. R³ 3-hydroxyl may be derivatised or converted to amino by conventional procedures.

R⁵-V'-CH₂-halides and R⁵-V'-CH₂-W derivatives, acyl derivatives R⁵CH₂COW and R⁵CH₂SO₂W or aldehydes R⁵-V'-CHO are commercially available or are prepared conventionally. The aldehydes may be prepared by partial reduction of the R⁵-V'-ester with lithium aluminium hydride or di-isobutylaluminium hydride or more preferably by reduction to the alcohol, with lithium aluminium hydride or sodium borohydride (see *Reductions by the Alumino- and Borohydrides in Organic Synthesis*, 2nd ed., Wiley, N.Y., 1997; *JOC*, 3197, 1984; *Org. Synth. Coll.*, 102, 1990; 136, 1998; *JOC*, 4260, 1990; *TL*, 995, 1988; *JOC*, 1721, 1999; *Liebigs Ann./Recl.*, 2385, 1997; *JOC*, 5486, 1987), followed by oxidation to the aldehyde with manganese (II) dioxide, or by a 'Swern' procedure (oxalyl chloride/DMSO), or by using potassium dichromate (PDC). The aldehydes may also be prepared from carboxylic acids in two stages by conversion to a mixed anhydride for example by reaction with isobutyl chloroformate followed by reduction with sodium borohydride (R. J. Alabaster *et al.*, *Synthesis*, 598, 1989) to give the alcohols and then oxidation with a standard oxidising agent such as pyridinium dichromate or by homologation of the R⁵CHO intermediate. Acyl derivatives R⁵CH₂COW may be prepared by activation of the R⁵-CH₂-ester. R⁵-V'-CH₂-halides such as bromides may be prepared from the alcohol R⁵-V'-CH₂OH by reaction with phosphorus tribromide in DCM/triethylamine. R⁵-V'-CH₂-W derivatives such as methanesulphonyl derivatives may be prepared from the alcohol R⁵-V'-CH₂OH by reaction with methane sulphonyl chloride. R⁵CH₂SO₂W derivatives may be prepared by a route analogous to that of Ahmed El Hadri *et al*, *J. Heterocyclic Chem.*, 1993, 30(3), 631. Thus compounds of formula R⁵CH₂SO₂OH may be prepared by reacting the corresponding R⁵CH₃ compound with N-bromosuccinimide, followed by treatment with sodium sulfite. The leaving group W may be converted to another leaving group W, e.g. a halogen group, by conventional methods. The R⁵-V'-U- derivatives may be prepared by various conventional strategies. For example the homologous aldehyde R⁵-CHO may be treated with trimethylsulfonium methylsulfate in basic conditions, to give an epoxide intermediate (see *Synth. Commun.*, 749, 1985) which is then treated with lewis acid, such as boron trifluorideetherate or diethyl etherate, to provide the desired aldehyde (see *JOC*,

1720, 1999). The aldehyde R^5 -CHO could also be treated with an appropriate phosphonium salt, such as (methoxymethyl)triphenylphosphonium chloride, in a Wittig fashion reaction. The resulting enol ether can readily be hydrolysed to homologous aldehydes (*Chem. Ber.*, 2514, 1962). R^5 -COW derivatives can be converted to the aldehyde R^5 -V'-CHO in several steps (see *JACS*, 1325, 1986). The R^5 COCH₂-halide derivatives may be prepared by standard methods from the R^5 CO₂H derivative, for example, by acid chloride formation, conversion to the alpha-diazoketone with diazomethane and reaction with a halogen acid to provide the halomethylketone.

Where R^5 is an optionally substituted benzoimidazol-2-yl group, the compound of formula (V) where $R^{4'}$ is R^4 may be obtained by reacting N protected piperidine with acrylonitrile, converting the resulting $R^{4'}$ 2-cyanoethyl group with partial hydrolysis to give the 2-ethoxycarbonimidoyl group which can then be condensed with an appropriately substituted 1,2-diaminobenzene to give the required benzoimidazol-2-yl group.

R^5 -H heterocycles are commercially available or may be prepared by conventional methods.

For example where a benzoxazinone is required, a nitrophenol may be alkylated with for example ethyl bromoacetate and the resulting nitro ester reduced with Fe in acetic acid (alternatively Zn/AcOH/HCl or H₂/Pd/C or H₂/Raney Ni). The resulting amine may undergo spontaneous cyclisation to the required benzoxazinone, or cyclisation may be induced by heating in acetic acid. Alternatively a nitrophenol may be reduced to the aminophenol, which is reacted with chloroacetyl chloride [method of X. Huang and C. Chan, *Synthesis* 851 (1994)] or ethyl bromoacetate in DMSO [method of Z. Moussavi et al. *Eur. J. Med. Chim. Ther.* 24, 55-60 (1989)]. The same general routes can be applied to prepare benzothiazinones [See for example F. Eiden and F. Meinel, *Arch. Pharm.* 312, 302-312 (1979), H. Fenner and R. Grauert *Liebigs. Ann. Chem.* 193-313 (1978)]. A variety of routes are available to prepare aza analogues of benzothiazinones via the key corresponding aldehydes. For instance, 2-oxo-2,3-dihydro-1H-pyrido[3,4-b][1,4]thiazine-7-carbaldehyde may be accessed from 5-fluoro-2-picoline (E. J. Blanz, F. A. French, J. R. DoAmaral and D. A. French, *J. Med. Chem.* 1970, 13, 1124-1130) by constructing the thiazinone ring onto the pyridyl ring then functionalising the methyl substituent, as described in the Examples. The dioxin analogue of this aza substitution pattern, 2,3-dihydro-[1,4]dioxino[2,3-c]pyridine-7-carbaldehyde is accessible from Kojic acid by aminolysis from pyrone to pyridone then annelating the dioxin ring, again as described in the subsequent experimental data. Other aza substitution patterns with pyridothiazin-3-one, pyridooxazin-3-one, and pyridodioxin ring systems are also accessible, again as described in the Examples. Ortho-aminothiophenols may be conveniently prepared and

reacted as their zinc complexes [see for example V. Taneja et al *Chem. Ind.* 187 (1984)]. Benzoxazolones may be prepared from the corresponding aminophenol by reaction with carbonyl diimidazole, phosgene or triphosgene. Reaction of benzoxazolones with diphosphorus pentasulfide affords the corresponding 2-thione. Thiazines and oxazines can be prepared by reduction of the corresponding thiazinone or oxazinone with a reducing agent such as lithium aluminium hydride.

Conversions of R^{1a'}, R^{1'}, R^{3'} and R^{4'} may be carried out on the intermediates of formulae (IV) and (V) prior to their reaction to produce compounds of formula (I) in the same way as described above for conversions after their reaction.

The pharmaceutical compositions of the invention include those in a form adapted for oral, topical or parenteral use and may be used for the treatment of bacterial infection in mammals including humans.

The antibiotic compounds according to the invention may be formulated for administration in any convenient way for use in human or veterinary medicine, by analogy with other antibiotics.

The composition may be formulated for administration by any route, such as oral, topical or parenteral. The compositions may be in the form of tablets, capsules, powders, granules, lozenges, creams or liquid preparations, such as oral or sterile parenteral solutions or suspensions.

The topical formulations of the present invention may be presented as, for instance, ointments, creams or lotions, eye ointments and eye or ear drops, impregnated dressings and aerosols, and may contain appropriate conventional additives such as preservatives, solvents to assist drug penetration and emollients in ointments and creams.

The formulations may also contain compatible conventional carriers, such as cream or ointment bases and ethanol or oleyl alcohol for lotions. Such carriers may be present as from about 1% up to about 98% of the formulation. More usually they will form up to about 80% of the formulation.

Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tableting lubricants, for example magnesium stearate, talc, polyethylene glycol or silica; disintegrants, for example potato starch; or acceptable wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in normal pharmaceutical practice. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid

preparations may contain conventional additives, such as suspending agents, for example sorbitol, methyl cellulose, glucose syrup, gelatin, hydroxyethyl cellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may
5 include edible oils), for example almond oil, oily esters such as glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and, if desired, conventional flavouring or colouring agents.

Suppositories will contain conventional suppository bases, e.g. cocoa-butter or other glyceride.

10 For parenteral administration, fluid unit dosage forms are prepared utilizing the compound and a sterile vehicle, water being preferred. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions the compound can be dissolved in water for injection and filter sterilised before filling into a suitable vial or ampoule and sealing.

15 Advantageously, agents such as a local anaesthetic, preservative and buffering agents can be dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. The dry lyophilized powder is then sealed in the vial and an accompanying vial of water for injection may be supplied to reconstitute the liquid prior to use. Parenteral suspensions
20 are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilization cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

25 The compositions may contain from 0.1% by weight, preferably from 10-60% by weight, of the active material, depending on the method of administration. Where the compositions comprise dosage units, each unit will preferably contain from 50-500 mg of the active ingredient. The dosage as employed for adult human treatment will preferably range from 100 to 3000 mg per day, for instance 1500 mg per day depending on the route
30 and frequency of administration. Such a dosage corresponds to 1.5 to 50 mg/kg per day. Suitably the dosage is from 5 to 20 mg/kg per day.

No toxicological effects are indicated when a compound of formula (I) or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof is administered in the above-mentioned dosage range.

35 The compound of formula (I) may be the sole therapeutic agent in the compositions of the invention or a combination with other antibiotics or with a β -lactamase inhibitor may be employed.

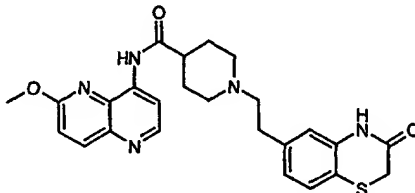
Compounds of formula (I) are active against a wide range of organisms including both Gram-negative and Gram-positive organisms.

The following examples illustrate the preparation of certain compounds of formula (I) and the activity of certain compounds of formula (I) against various bacterial organisms.

5

Examples

Example 1 1-[2-(3-Oxo-3,4-dihydro-2H-benzo[1,4]thiazin-6-yl)-ethyl]-piperidine-4-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide oxalate



5 (a) 6-Methoxy-1 *H*-[1,5]naphthyridin-4-one

A solution of 5-amino-2-methoxypyridine (50g, 0.4 mol) in ethanol (300ml) was treated with 2,2-dimethyl-[1,3]dioxane-4,6-dione (Meldrum's acid) (68g) and triethylorthoformate (66 ml). The mixture was heated to reflux for 2 hours, then allowed to cool. Filtration afforded the intermediate 5-[(6-methoxy-pyridin-3-ylamino)-methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione as a white solid (101.2g). A portion of this material (50g) was added to boiling Dowtherm A (300 ml) over 3 minutes under a stream of argon. The mixture was refluxed for a further 5 minutes then allowed to cool before adding to ether. Filtration and drying afforded 6-methoxy-1 *H*-[1,5]naphthyridin-4-one as a white solid (24.7 g, 70%).

15 MS (+ve ion electrospray) m/z 177 (MH⁺).

(b) 1,1,1-Trifluoro-methanesulfonic acid 6-methoxy-[1,5]naphthyridin-4-yl ester

A suspension of naphthyridone (a) (10g, 0.057mol) in dichloromethane (200 ml) containing 2,6-lutidine (9.94 ml, 86 mmol) and 4-dimethylaminopyridine (0.07g, 5.7 mol) was cooled in ice and treated with trifluoromethanesulfonic anhydride (10.5 ml, 63 mmol). After stirring for 2.5 hours the mixture was washed with saturated ammonium chloride solution, dried, evaporated and purified on silica eluting with dichloromethane affording the triflate as an oil (13.4 g, 76%).

20 MS (+ve ion electrospray) m/z 309 (MH⁺).

25

(c) 6-Methoxy-[1,5]naphthyridin-4-ylamine

A mixture of triflate (b) (25g, 81.2 mmol) and propylamine hydrochloride (47g, 487 mmol) in pyridine (300 ml) was heated to reflux overnight. The mixture was evaporated to dryness, dissolved in 0.5M aqueous hydrochloric acid (400 ml) and extracted three times with dichloromethane. The aqueous phase was then basified with 40% aqueous sodium hydroxide solution and extracted twice with dichloromethane. Drying and evaporation afforded a buff coloured solid (13.0g, 90%).

30 MS (+ve ion electrospray) m/z 176 (MH⁺).

(d) Piperidine-1,4-dicarboxylic acid benzyl ester

A solution of piperidine-4-carboxylic acid (4.7g, 36 mmol) in 0.5M aqueous sodium hydroxide (160 ml, 80 mmol) and dioxan (50 ml) was treated with benzyl chloroformate (4.3 ml, 5.13g, 30 mmol). After 1 hour the mixture was acidified with 5M aqueous hydrochloric acid and extracted twice with ethyl acetate. The combined organic extracts were washed with water and brine, then dried and evaporated affording an oil (7.9g, 100%).

MS (+ve ion electrospray) m/z 264 (MH+).

10

(e) 4-(6-Methoxy-[1,5]naphthyridin-4-ylcarbamoyl)-piperidine-1-carboxylic acid benzyl ester

A solution of acid (d) (7.9g, 30 mmol) and triethylamine (4.2 ml, 3.03g, 30 mmol) in N,N-dimethylformamide (50 ml) was treated with [O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate] (HATU) (9.5g, 25 mmol). After 0.25 hours, amine (c) (3.5g, 20 mmol) was added and the mixture heated at 50°C overnight. Evaporation afforded an oil which was partitioned between ethyl acetate and dilute brine. Drying and evaporation afforded an oil (10g) which was chromatographed on silica eluting with a 0-5% methanol in ethyl acetate gradient, affording an oil (6.0g, 80%).

20 MS (+ve ion electrospray) m/z 421 (MH+).

(f) Piperidine-4-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide

A solution of (e) (6.0g, 14.3 mmol) in ethanol/ethyl acetate (150 ml/150 ml) was hydrogenated over 10% Pd/charcoal (5g) for 1.5 hours. Filtration, washing with ethanol (400 ml) and evaporation of the filtrate gave a white solid (2.4g, 59%).

MS (+ve ion electrospray) m/z 287 (MH+).

(g) [4-(2-Hydroxy-ethyl)-2-nitro-phenylsulfanyl]-acetic acid.

A mixture of 2-(4-fluoro-3-nitro-phenyl)-ethanol [RN20274-69-5] (1.1 g, 6 mmol), mercaptoacetic acid (0.61 g, 6.6 mmol), potassium carbonate (2.8 g, 20 mmol) and N,N-dimethylformamide (12 ml) was heated at 70°C for 4 hours. The mixture was poured onto water (200 ml) and the aqueous phase was washed with ethyl acetate. The aqueous phase was then acidified with 1M aqueous hydrochloric acid and extracted three times with dichloromethane. The extracts were dried and evaporated to give an oil (0.92 g, 60%).

35

δ H (d-6 DMSO, 200MHz): 8.07 (1H, d), 7.60 (1H, dd), 7.50 (1H, d), 3.92 (2H, s), 3.63 (2H, t), 3.50 (2H, br), 2.79 (2H, t).

(h) 6-(2-Hydroxy-ethyl)-4*H*-benzo[1,4]thiazin-3-one.

A mixture of iron powder (1.24 g, 22 mmol) and sodium chloride (1.24 g, 21 mmol) in 50% aqueous ethanol (25 ml) was heated under reflux for 15 minutes. A solution of crude
5 (g) (0.92 g, 3.6 mmol) in ethanol (5 ml) was then added quickly and the reaction mixture was heated under reflux for 2 hours. The mixture was filtered through keiselguhr and the solution was evaporated to dryness. The residue was dissolved in water and acidified to pH5 with 1M aqueous hydrochloric acid. The precipitate was collected by filtration, washed with water, then dried to give a white solid (0.35 g, 46%).
10 δ H (d-6 DMSO, 200MHz): 10.48 (1H, br), 7.20 (1H, d), 6.92-6.87 (2H, m), 4.65 (1H, t), 3.56 (2H, q), 3.42 (2H, s), 2.64 (2H, t).

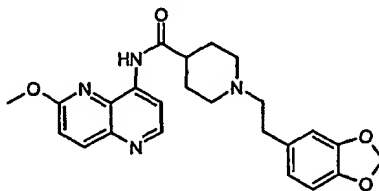
(i) Methanesulfonic acid 2-(3-oxo-3,4-dihydro-2*H*-benzo[1,4]thiazin-6-yl)-ethyl ester

A solution of (h) (0.34g, 1.7 mmol) and triethylamine (0.25 ml, 0.19 g, 1.8 mmol)
15 in dichloromethane (5 ml) was cooled to -15°C and treated dropwise with methanesulfonyl chloride (0.14 ml, 1.75 mmol). The ice bath was removed and the mixture stirred 15 hours at room temperature. The organic phase was separated, washed with water, dried over magnesium sulfate and evaporated. The crude product was chromatographed on silica gel eluting with ethyl acetate/heptane (2/1) to give a white
20 solid (0.36 g, 75%).
 δ H (d-6 DMSO, 200MHz): 10.55 (1H, br), 7.27 (1H, d), 6.92 (1H, dd), 6.87 (1H, d), 4.37 (2H, t), 3.45 (2H, s), 3.13 (3H, s), 2.93 (2H, t).

(j) Title compound

A mixture of amine (f) (0.15g, 0.52 mmol), mesylate (i) (0.158 g, 0.55 mmol) and potassium carbonate (0.076g, 0.55 mmol) in *N,N*-dimethylformamide (3 ml) was stirred at 40°C for 8 hours. The mixture was diluted with water and ethyl acetate. The insoluble residue was collected by filtration, washed with water and ethyl acetate, then dried to give the free base of the title compound as a white solid (0.15 g, 25%).
25
30 δ H (d-6 DMSO, 200MHz): 10.62 (1H, br), 9.91 (1H, br), 8.70 (1H, d), 8.40 (1H, d), 8.28 (1H, d), 7.42-7.24 (2H, m), 7.00-6.78 (2H, m), 4.15 (3H, s), 3.60 (2H, m), 3.44 (2H, s), 3.22 (2H, m), 3.13-2.81 (5H, m), 2.30-1.85 (4H, m).
MS (+ve ion electrospray) m/z 478 (MH⁺).
A suspension of the above solid (55 mg, 0.12 mmol) in acetone was treated with a
35 solution of oxalic acid (22 mg) in acetone and the mixture was stirred for 2 hours. The precipitate was collected by filtration to give the title compound as white crystals (58 mg).

Example 2 1-(2-Benzo[1,3]dioxol-5-yl-ethyl)-piperidine-4-carboxylic acid (6-methoxy-1,5-naphthyridin-4-yl)-amide, dioxalate



5 (a) 2-Benzo[1,3]dioxol-5-yl-ethanol

A solution of benzo[1,3]dioxol-5-yl-acetic acid (2.5g, 13.9 mmol) in tetrahydrofuran (15 ml) under argon at -10°C was treated dropwise with borane-dimethylsulfide complex (1.45 ml, 15.3 mmol). The mixture was stirred at ambient temperature for 1.5 hours (CAUTION – exothermic reaction). The orange solution was cooled to $\sim 5^{\circ}\text{C}$ (ice bath) and methanol (1.4 ml) was added. After 0.5 hour at room temperature, the mixture was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate solution. The organic extract was dried and evaporated to give a yellow oil (1.95g, 84%).

MS (+ve ion electrospray) m/z 167 (MH⁺).

15

(b) Methanesulfonic acid 2-benzo[1,3]dioxol-5-yl-ethyl ester

A solution of alcohol (a) (1.90g, 11 mmol) in dichloromethane (25 ml) was treated at 0°C with triethylamine (1.9 ml, 13.7 mmol) and methanesulfonyl chloride (1.1 ml, 13.7 mmol). After 1.5 hours at room temperature the mixture was partitioned between dichloromethane and water. The organic extract was dried and evaporated to give a yellow oil (2.7g, 96%).

MS (+ve ion electrospray) m/z 245 (MH⁺).

(c) Title compound

25 This was prepared from amine (1f) (0.15g), mesylate (b) (0.134 g) and potassium carbonate (0.076 g) in N,N-dimethylformamide (3 ml) at 50°C for 6 hours in a similar procedure to that of Example (1j). The solvent was evaporated in vacuo and the residue was dissolved in ethyl acetate, washed with water, dried over magnesium sulfate and evaporated to dryness. The residue was chromatographed on silica gel eluting with ethyl acetate/methanol (95/5) to give the free base of the title compound as an oil (70 mg, 31%).

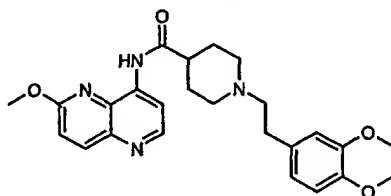
30

δH (d-6 DMSO, 200MHz): 9.91 (1H, br), 8.70 (1H, d), 8.40 (1H, d), 8.28 (1H, d), 7.33 (1H, d), 6.94-6.85 (2H, m), 6.76 (1H, dd), 6.00 (2H, s), 4.16 (3H, s), 3.58 (2H, m), 3.23 (2H, m), 3.17-2.83 (5H, m), 2.29-1.88 (4H, m).

MS (+ve ion electrospray) m/z 435 (MH⁺).

This was converted to the title compound (61 mg) by treating with oxalic acid in acetone according to the procedure for Example 1.

5 Example 3 1-[2-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-ethyl]-piperidine-4-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide, dioxalate



(a) 6-Oxiranyl-2,3-dihydro-benzo[1,4]dioxine

A mixture of 1,4-benzodioxanecarboxaldehyde [RN 29668-44-8] (1.5 g, 9.14 mmol), trimethylsulfonium methyl sulfate (2.24 g, 11.9 mmol), dichloromethane (35 ml) and 50% aqueous sodium hydroxide (5 ml) were vigorously stirred for 70 hours. The mixture was partitioned between water and diethyl ether and the layers separated. The aqueous phase was extracted with diethyl ether. The combined organic phases were washed with water, brine, then dried over magnesium sulfate and evaporated to give crude 6-oxiranyl-2,3-dihydro-benzo[1,4]dioxine (1.64g, 100%).
 δ H (CDCl₃, 200MHz): 6.88-6.72 (3H, m), 4.25 (4H, s), 3.76 (1H, dd), 3.10 (1H, dd), 2.77 (1H, dd).

(b) (2,3-Dihydro-benzo[1,4]dioxin-6-yl)-acetaldehyde.

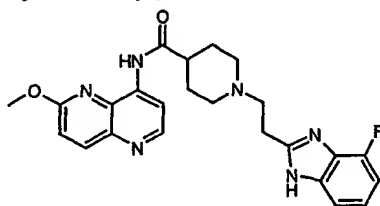
A solution of crude 6-oxiranyl-2,3-dihydro-benzo[1,4]dioxine (200 mg, 1.12 mmol) in diethyl ether (20 ml) was cooled at -10°C. A 10% solution of boron trifluoride diethyl etherate in diethyl ether (0.16ml) was then added and the mixture was stirred for 10 minutes at -10°C. The reaction was quenched at this temperature by addition of a saturated aqueous solution of sodium bicarbonate (10 ml). The mixture was extracted twice with diethyl ether. The combined organic phases were washed with water, brine, then dried over magnesium sulfate and evaporated to give crude (2,3-dihydro-benzo[1,4]dioxin-6-yl)-acetaldehyde (191 mg, 95%).
 δ H (CDCl₃, 200MHz): 9.70 (1H, t), 6.95-6.62 (3H, m), 4.26 (4H, s), 3.56 (2H, d).

(c) Title compound

A solution of amine (1f) (238 mg, 0.83 mmol) and crude aldehyde (3b) (191 mg, 1.07 mmol) in methanol (20 ml) was acidified to pH5 with a few drops of acetic acid then sodium cyanoborohydride (42 mg, 0.67 mmol) was added and the mixture was stirred for 20 hours. The solvent was evaporated and the residue was triturated with ethyl acetate (10

- ml) and 0.1M aqueous sodium hydroxide solution (10 ml). The mixture was filtered and the layers of the filtrate were separated. The aqueous phase was extracted with more ethyl acetate. The combined organic extracts were washed with water, dried over magnesium sulfate and evaporated to give a solid (0.2g). This solid was triturated with heptane-ethyl acetate (2-1) to give the free base of the title compound (85 mg, 23%).
- δ H (d-6 DMSO, 200MHz): 9.79 (1H, br), 8.67 (1H,d), 8.41 (1H, d), 8.27 (1H, d), 7.32 (1H, d), 6.81-6.60 (3H, m), 4.20 (4H, s), 4.13 (3H, s), 2.99 (2H,m), 2.82-2.48 (5H, m), 2.15-1.85 (4H, m), 1.84-1.58 (2H, m).
- MS (+ve ion electrospray) m/z 449 (MH+).
- This was converted to the title compound (112 mg) by treating with oxalic acid in acetone according to the procedure for Example 1.

Example 4 1-[2-(4-Fluoro-1H-benzimidazol-2-yl)-ethyl]-piperidine-4-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide, dioxalate



- (a) 1-(2-Cyano-ethyl)-piperidine-4-carboxylic acid ethyl ester
- A solution of piperidine-4-carboxylic acid ethyl ester (ethylisonipecotrate) (4.7 g, 30 mmol), acrylonitrile (1.7 g, 31 mmol) in isopropyl alcohol (30 ml) was stirred at room temperature for 15 hours, then evaporated to dryness to afford 1-(2-cyano-ethyl)-piperidine-4-carboxylic acid ethyl ester as an oil (6.4 g, 100%).
- δ H (CDCl₃, 200MHz): 4.13(2H, q), 2.94-2.78 (2H, m), 2.75-2.62 (2H, m), 2.55-2.43 (2H, m), 2.27 (1H,m), 2.14 (2H, m), 1.99-1.62 (4H, m), 1.25 (3H, t).
- (b) 1-[2-(4-Fluoro-1H-benzimidazol-2-yl)-ethyl]-piperidine-4-carboxylic acid ethyl ester
- A solution of (a) (6.4 g, 30 mmol) and ethanol (2.1 ml, 40 mmol) in chloroform (60 ml) was saturated with gaseous hydrochloric acid at 0°C for 0.5 hours. The mixture was left 20 hours at 4°C then concentrated in vacuo to afford a white foam. This was suspended in chloroform (60 ml), treated with 3-fluorophenylenediamine (3.8 g, 30 mmol) and heated under reflux for 1 hour. The mixture was poured onto water. The aqueous phase was then basified with sodium bicarbonate and extracted three times with dichloromethane. The organic extract was washed with water, brine, dried over magnesium sulfate and evaporated. The resulting residue was triturated with ethyl acetate, then diethyl ether to give a white solid (5.2 g, 55%).

δ H (CDCl₃, 200MHz): 7.29 (1H, d), 7.21-7.05 (1H, m), 7.00-6.82 (1H, m), 4.17 (2H, q), 3.12-2.95 (4H, m), 2.88 (1H, br), 2.80 (2H, t), 2.42 (1H, m), 2.31-1.73 (6H, m), 1.29 (3H, t).

5 (c) 1-[2-(4-Fluoro-1*H*-benzimidazol-2-yl)-ethyl]-piperidine-4-carboxylic acid.

A solution of (b) (2.0g, 6.3 mmol), 1M aqueous sodium hydroxide solution (1.2 ml, 1.2 mmol) in ethanol (40 ml) was stirred at room temperature for 3 hours. After concentration, the residue was diluted with water and acidified with a saturated solution of potassium hydrogenosulfate to pH 5. The precipitated solid was filtered, washed with
10 water and dried under vacuum to afford a foam (1.0g, 54%).

δ H (d-6 DMSO, 200MHz): 7.28 (1H, d), 7.21-7.02 (1H, m), 7.00-6.81 (1H, m), 3.41 (2H, br), 3.10-2.62 (6H, m), 2.33-1.95 (3H, m), 1.94-1.68 (2H, m), 1.65-1.40 (2H, m).

(d) Title compound

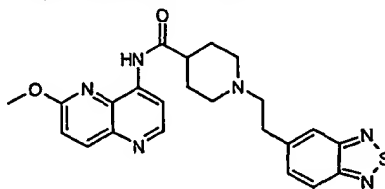
15 A mixture of (c) (291 mg, 1 mmol), [O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate] (HATU) (570 mg, 1.5 mmol), amine (1c) (0.176g, 1 mmol) and triethylamine (0.21 ml, 1.5 mmol) in tetrahydrofuran/dichloromethane (15 ml/12 ml) was stirred at room temperature for 16 hours. After concentration, the residue was heated in dimethylsulfoxide (8 ml) for 4
20 hours, then poured into water, basified with 1M aqueous sodium hydroxide, and extracted three times with dichloromethane. The organic phase was washed with water, brine, dried over magnesium sulfate and evaporated. The product was purified by column chromatography on silica gel, eluting with ethyl acetate-methanol (9:1) to afford the free base of the title compound as a white solid (90 mg, 20%).

25 δ H (d-6 DMSO, 200MHz): 12.5 (1H, br), 9.78 (1H, s), 8.67 (1H, d), 8.41 (1H, d), 8.26 (1H, d), 7.38-7.23 (2H, m), 7.10 (1H, m), 6.92 (1H, dd), 4.13 (3H, s), 3.10-2.91 (4H, m), 2.90-2.62 (3H, m), 2.22-2.03 (2H, m), 2.01-1.87 (2H, m), 1.86-1.55 (2H, m).

MS (+ve ion electrospray) m/z 449 (MH⁺).

This was converted to the title compound (60 mg) by treating with oxalic acid in acetone
30 according to a similar procedure as for Example 1.

Example 5 1-(2-Benzo[1,2,5]thiadiazol-5-yl-ethyl)-piperidine-4-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide, dioxalate



(a) Benzo[1,2,5]thiadiazol-5-yl-acetonitrile

A mixture of 5-bromomethyl-benzo[1,2,5]thiadiazole [RN65858-50-6] (7.0 g, 30 mmol), ethanol (50 ml) and a solution of potassium cyanide (2.3 g, 36 mmol) in water (25 ml) was stirred at 50°C for 15 hours. The alcoholic solution was concentrated and the residue suspended in water. The solid was collected by filtration, washed with water and dried in *vacuo* to give benzo[1,2,5]thiadiazol-5-yl-acetonitrile (2.8 g, 47%)

(b) Benzo[1,2,5]thiadiazol-5-yl-acetic acid

A suspension of benzo[1,2,5]thiadiazol-5-yl-acetonitrile (a) (2.8 g, 14 mmol) in 6N aqueous hydrochloric acid (70 ml) was heated under reflux for 4 hours. The mixture was cooled to room temperature and diluted with more water. The precipitate was collected by filtration, washed with water and dried in *vacuo* to give crude benzo[1,2,5]thiadiazol-5-yl-acetic acid (2.8 g, 100%).

δ H(DMSO- d_6 , 200MHz): 12.58 (1H, br), 8.03 (1H, d), 7.97 (1H, d), 7.65 (1H, dd), 3.86 (2H, s).

(c) 2-Benzo[1,2,5]thiadiazol-5-yl-ethanol.

Borane methylsulfide (1.6 ml) was added dropwise to a cold solution (8-10°C) of crude benzo[1,2,5]thiadiazol-5-yl-acetic acid (b) (2.8 g, 14 mmol) in tetrahydrofuran (20 ml). Stirring was continued for 1.25 hours while maintaining the temperature below 30°C. The mixture was cooled to 10°C then methanol was added (1.4 ml) and the mixture was left 15 hours in the refrigerator. The mixture was diluted with ethyl acetate, washed with water then with a saturated aqueous solution of sodium hydrogencarbonate and again with water. The organic phase was separated, dried over magnesium sulfate and evaporated.

The residue was triturated in pentane, collected by filtration and dried to give crude 2-benzo[1,2,5]thiadiazol-5-yl-ethanol (1.8 g, 71%).

δ H(CDCl₃, 200MHz): 7.94 (1H, d), 7.84 (1H, d), 7.50 (1H, dd), 3.99 (2H, t), 3.06 (2H, t), 1.58 (1H, br).

(d) Methanesulfonic acid 2-benzo[1,2,5]thiadiazol-5-yl-ethyl ester.

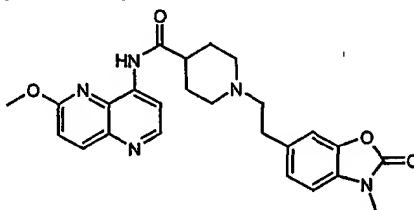
Methanesulfonyl chloride (0.45 ml, 5.8 mmol) was added dropwise to an ice-cooled solution of 2-benzo[1,2,5]thiadiazol-5-yl-ethanol (c) (1.0 g, 5.5 mmol) and triethylamine (0.85 ml, 6 mmol) in dichloromethane (20 ml). The reaction mixture was allowed to warm to room temperature and stirred for 16 hours. The organic solution was washed with water, dried over magnesium sulfate and evaporated to dryness. The oily residue was triturated with diisopropyl ether. The solid was collected by filtration and

dried to give methanesulfonic acid 2-benzo[1,2,5]thiadiazol-5-yl-ethyl ester (1.2 g, 78%) which was used without further purification in the next step.

(e) Title compound.

- 5 A mixture of piperidine-4-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide (1f) (0.2 g, 0.7 mmol), mesylate (d) (0.2 g, 0.77 mmol), triethylamine (0.11 ml) and acetonitrile (12 ml) was heated under reflux for 16 hours. After cooling to room temperature the mixture was poured onto water and extracted with ethyl acetate. The organic phase was washed with water, dried over magnesium sulfate and evaporated to dryness. The crude product was chromatographed on silica gel eluting with methylene chloride-methanol (95-5). The product was triturated in ethyl acetate and filtered to give the free base of the title compound as a solid (0.16 g, 41%).
- 10 δ H(d-6 DMSO, 200MHz): 9.78 (1H, s), 8.67 (1H, d), 8.40 (1H, d), 8.26 (1H, d), 8.01 (1H, d), 7.93 (1H, d), 7.66 (1H, dd), 7.31 (1H, d), 4.13 (3H, s), 3.15-2.90 (4H, m), 2.86-2.08 (3H, m), 2.11 (2H, m), 1.95 (2H, m), 1.72 (2H, m).
- 15 This was converted to the title compound (130 mg) by treating with oxalic acid in acetone according to the procedure for Example 1, mp : 228-230°C.

- 20 **Example 6 1-[2-(3-Methyl-2-oxo-2,3-dihydro-benzooxazol-6-yl)-ethyl]-piperidine-4-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide, dioxalate**



(a) 6-(2-Hydroxy-ethyl)-3-methyl-3H-benzooxazol-2-one.

- Borane dimethylsulfide complex (10M; 1.1 ml, 11 mmol) was added dropwise to a cold suspension (10°C) of (3-methyl-2-oxo-2,3-dihydro-benzooxazol-6-yl)-acetic acid [RN245095-56-1] (2.1 g, 10 mmol) in anhydrous tetrahydrofuran (20 ml). The reaction temperature was allowed to rise progressively to 28-29°C. After 1 hour the temperature began to decrease. Stirring was maintained for a further 0.5 hour, then the mixture was cooled to 10°C and treated dropwise with methanol (1 ml). Stirring was continued, at room temperature, for another 0.5 hour. The reaction mixture was concentrated and the residue was suspended in water and the aqueous phase was acidified by 0.1 N hydrochloric acid. The solid (unreacted starting acid) was filtered off. The aqueous phase was extracted three times with dichloromethane. The extract was dried over magnesium
- 25
- 30

sulfate and evaporated. The crude residue was chromatographed on silica gel eluting with dichloromethane-methanol (95-5) to give the product (0.78 g, 80% based on reacted acid). δ H(CDCI₃, 200MHz): 7.10 (1H, d), 7.07 (1H, dd), 6.89 (1H, d), 3.86 (2H, t), 3.39 (3H, s), 2.90 (2H, t).

5

(b) Methanesulfonic acid 2-(3-methyl-2-oxo-2,3-dihydro-benzooxazol-6-yl)-ethyl ester.

Methanesulfonyl chloride (0.14ml, 1.75 mmol) was added dropwise to an ice cooled solution of (6a) (325 mg, 1.7 mmol) and triethylamine (0.25 ml, 1.8 mmol) in dichloromethane (5 ml). The reaction mixture was allowed to warm to room temperature and stirred for 15 hours. The organic solution was washed with water, dried over magnesium sulfate and evaporated to dryness. The residue was triturated with diisopropyl ether. The solid was collected by filtration and dried to give the product (410 mg, 89%) δ H(CDCI₃, 200MHz): 7.14-7.02 (2H, m), 6.91 (1H, d), 4.40 (2H, t), 3.40 (3H, s), 3.09 (2H, t), 2.93 (3H, s).

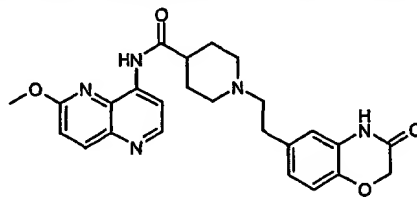
15

(c) Title compound.

A mixture of amine (1f) (0.2 g, 0.7 mmol), mesylate (b) (0.19 g, 0.7 mmol), triethylamine (0.11 ml) and acetonitrile (12 ml) was heated under reflux for 20 hours. After cooling the mixture was poured onto water and extracted twice with dichloromethane. The organic phase was washed with water, dried over magnesium sulfate and evaporated to dryness. The crude product was chromatographed on silica gel eluting with methylene chloride-methanol (95-5). to give the free base of the title compound (0.115 g, 35%) as a solid. δ H(d-6 DMSO, 200MHz): 9.78 (1H, s), 8.67 (1H, d), 8.40 (1H, d), 8.26 (1H, d), 7.31 (1H, d), 7.24 (1H, d), 7.20-7.02 (2H, m), 4.13 (3H, s), 3.29 (3H, s), 3.00 (2H, m), 2.87-2.63 (3H, m), 2.53 (2H, m), 2.20-1.54 (6H, m). This was converted to the title compound (131 mg) by treating with oxalic acid in acetone according to the procedure for Example 1, mp : 226-228°C.

25

30 **Example 7 1-[2-(3-Oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl)-ethyl]-piperidine-4-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide, dioxalate**



(a) 6-(2-Hydroxy-ethyl)-4H-benzo[1,4]oxazin-3-one.

Lithium aluminium hydride (0.7 g, 14.6 mmol) was added portionwise to an ice-cooled solution of (3-oxo-3,4-dihydro-2*H*-benzo[1,4]oxazin-6-yl)-acetic acid tert-butoxycarbonylmethyl ester [RN134997-90-3] (4.5 g, 14 mmol) in tetrahydrofuran (100 ml). The mixture was allowed to warm to room temperature and stirring was maintained for 1 hour. The excess of hydride was hydrolysed by careful addition of a saturated aqueous solution of ammonium chloride (10 ml). The mixture was filtered and the filtrate was evaporated. The residue was triturated with diisopropyl ether to give the product (2.15 g, 80%).

δ H(CDCI₃, 200MHz): 10.63 (1H, s), 6.85-6.70 (3H, m), 4.62 (1H, t), 4.51 (2H, s), 3.53 (2H, t), 2.62 (2H, t).

(b) Methanesulfonic acid 2-(3-oxo-3,4-dihydro-2*H*-benzo[1,4]oxazin-6-yl)-ethyl ester.

A solution of alcohol (a) (0.65 g, 3.38 mmol) and triethylamine (0.52 ml, 3.72 mmol) in tetrahydrofuran (30 ml) was cooled to -10°C and treated dropwise by methanesulfonyl chloride (0.26 ml, 3.6 mmol). The ice bath was removed and the mixture stirred 20 hours at room temperature. More triethylamine (0.6 ml) and methane sulfonyl chloride (0.3 ml) were added at 0°C and the mixture stirred for a further 2 hours. The mixture was diluted with ethyl acetate and washed with water. The organic phase was dried over magnesium sulfate and evaporated. The crude product was chromatographed on silica gel eluting with methylene chloride-methanol (98-2) to give the product (0.85 g, 92%).

δ H(CDCI₃, 200MHz): 8.63 (1H, s), 6.91 (1H, s), 6.87 (1H, d), 6.72 (1H, d), 4.61 (2H, s), 4.41 (2H, t), 3.01 (2H, t), 2.94 (3H, s).

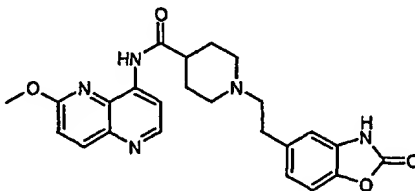
(c) Title compound.

A mixture of amine (1f) (0.58 g, 2 mmol), mesylate (b) (0.6 g, 2.2 mmol), potassium carbonate (0.3 g, 2.2 mmol) and acetonitrile (40 ml) was heated under reflux for 6 hours and stirred at room temperature for 48 hours. The mixture was poured into water and extracted twice with dichloromethane. The organic phase was washed with water, dried over magnesium sulfate and evaporated to dryness. The crude product was chromatographed on silica gel eluting with dichloromethane-methanol (98-2) to give the free base of the title compound (0.25 g, 27%).

δ H(d-6 DMSO, 200MHz): 10.65 (1H, br), 9.79 (1H, s), 8.68 (1H, d), 8.41 (1H, d), 8.27 (1H, d), 7.31 (1H, d), 6.93-6.70 (3H, m), 4.52 (2H, s), 4.14 (3H, s), 3.01 (2H, m), 2.82-2.58 (3H, m), 2.50 (2H, m), 2.20-1.75 (6H, m).

This was converted to the title compound (290 mg) by treating with oxalic acid in acetone according to the procedure for Example 1, mp: 230°C.

Example 8 1-[2-(2-Oxo-2,3-dihydro-benzoxazol-5-yl)-ethyl]-piperidine-4-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide, dioxalate



5 (a) (2-Oxo-2,3-dihydro-benzoxazol-5-yl)-acetic acid ethyl ester.

A mixture of (3-amino-4-hydroxy-phenyl)-acetic acid ethyl ester [RN86818-19-1] (1.0 g, 5.12 mmol), urea (1.53 g, 25.5 mmol) and N,N-dimethylformamide (16 ml) was heated under reflux for 4 hours. The solvent was partly evaporated, the mixture was poured onto ice water and acidified with 1N hydrochloric acid. The precipitate was collected by filtration, washed with water and dried *in vacuo* to give the product (1.0 g, 75%).

δ H(d-6 DMSO, 200MHz): 11.35 (1H, br), 7.21 (1H, d), 7.01 (1H, s), 6.96 (1H, d), 4.08 (2H, q), 3.68 (2H, s), 1.18 (3H, t).

15 (b) 5-(2-Hydroxy-ethyl)-3H-benzoxazol-2-one.

Ester (a) (0.95 g, 4.29 mmol) was added portionwise to a cold solution (0°C) of lithium aluminium hydride (0.206 g, 4.7 mmol) in tetrahydrofuran (20 ml). The mixture was then stirred 1.5 hours at room temperature and cooled again. The excess of hydride was hydrolysed by careful addition of water (0.2 ml), 5N aqueous sodium hydroxide solution (0.2 ml) and finally water (0.6 ml). Magnesium sulfate was added and the mixture was filtered. The filtrate was concentrated to dryness to give the product (0.5 g, 65%).

δ H(d-6 DMSO, 200MHz): 6.91 (1H, d), 6.78 (1H, s), 6.65 (1H, d), 6.56 (1H, s), 3.56 (2H, t), 2.66 (2H, t).

25

(c) Methanesulfonic acid 2-(2-oxo-2,3-dihydro-benzoxazol-5-yl)-ethyl ester.

Methanesulfonyl chloride (0.23 ml, 2.93 mmol) was added dropwise, at room temperature, to a solution of alcohol (b) (0.5 g, 2.79 mmol) and triethylamine (0.41 ml, 3 mmol) in tetrahydrofuran (20 ml) and the mixture was stirred for 3 hours. More methane sulfonyl chloride (0.1 ml) and triethylamine (0.1 ml) were added and stirring was continued over night. The same amount of reagent was added yet again and stirring continued for 2 hours. The solvent was then concentrated, the residue was suspended in water and extracted with dichloromethane. The organic phase was dried over magnesium

30

sulfate and concentrated. The solid residue was chromatographed on silica gel eluting with heptane-ethyl acetate (1-1) to give the product (0.2 g, 28%).

δ H(d-6 DMSO, 200MHz): 7.22 (1H, d), 7.04 (1H, s), 7.00 (1H, d), 4.40 (2H, t), 3.12 (3H, s), 3.01 (2H, t).

5

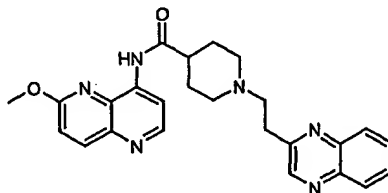
(d) Title compound.

A mixture of amine (1f) (0.234 g, 0.82 mmol), mesylate (c) (0.21 g, 0.82 mmol), potassium carbonate (0.124 g, 0.9 mmol) and acetonitrile (15 ml) was heated under reflux for 5 hours. The solvent was concentrated, the residue was suspended in water and
10 extracted with dichloromethane. The organic phase was dried over magnesium sulfate and concentrated. The solid residue was chromatographed on silica gel eluting with dichloromethane-methanol (95-5) to give the free base of the title compound (29 mg, 8%).

δ H(d-6 DMSO, 200MHz): 9.75 (1H, br), 8.66 (1H, d), 8.40 (1H, d), 8.25 (1H, d), 7.29
15 (1H, d), 7.16 (1H, dd), 7.00-6.82 (2H, m), 4.12 (3H, s), 3.50 (1H, br), 3.00 (2H, m), 2.85-2.62 (3H, m), 2.50 (2H, m), 2.20-1.87 (4H, m), 1.74 (2H, m).

This was converted to the title compound (32 mg) by treating with oxalic acid in acetone according to the procedure for Example 1, mp : 180°C.

20 **Example 9 1-(2-Quinoxalin-2-yl-ethyl)-piperidine-4-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide**



(a) Diethyl-(2-quinoxalin-2-yl-ethyl)-amine.

A solution of diethylamine hydrochloride (3.82 g, 35 mmol) and triethylamine
25 (0.23 ml) in ethanol (1.75 ml) and water (1.75 ml) was added dropwise, at 60°C, to a mixture of 2-methyl-quinoxaline (5.0 g, 35 mmol), formaldehyde (2.81 g of 37% solution, 35 mmol), triethylamine (0.17 ml) and ethanol (4.6 ml). The pH was adjusted to 7-7.5 by mean of dilute aqueous hydrochloric acid.. Stirring was maintained 16 hours at 60°C. The solvent was concentrated, the residue was diluted with water and extracted
30 with diethyl ether to remove the unreacted quinoxaline. The aqueous phase was basified with 20% aqueous sodium hydroxide (10 ml) and extracted with ethyl acetate. The organic phase was dried over magnesium sulfate and concentrated. The residue was chromatographed on silica gel eluting with dichloromethane-methanol (first 95-5 then 90-

10 and finally 90-10 plus 0.1% of ammonia) to give diethyl-(2-quinoxalin-2-yl-ethyl)-amine (2.67 g, 37%).

δ H(CDCI₃, 200MHz): 8.78 (1H, s), 8.05 (2H, m), 7.72 (2H, m), 3.17 (2H, m), 3.00 (2H, m), 2.64 (4H, q), 1.05 (6H, t).

5

(b) 2-Vinyl-quinoxaline.

Dimethyl sulfate (1.07 ml, 11.3 mmol) was added dropwise, while maintaining the mixture temperature below 40°C, to a solution of amine (a) (2.6g 11.3 mmol) in ethanol (3 ml). The thick mixture was diluted with water (15 ml) then triethylamine (1.13 ml) was
10 added and the mixture heated for 2 hours on a water bath. After cooling the mixture was extracted with diethyl ether. The organic phase was dried over magnesium sulfate, concentrated to dryness and the residue was chromatographed on silica eluting with heptane-ethyl acetate (3-1) to give the product (1.16 g, 66%).

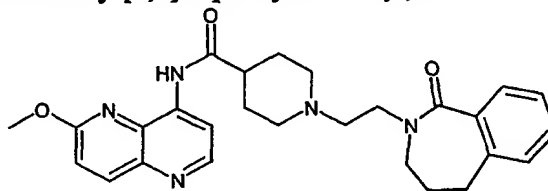
δ H(CDCI₃, 200MHz): 9.00 (1H, s), 8.07 (2H, m), 7.75 (2H, m), 7.05 (1H, dd), 6.48 (1H, 15 dd), 5.80 (1H, dd).

(c) Title compound.

A mixture of amine (1f) (0.403 g, 1.4 mmol), 2-vinyl-quinoxaline (b), (0.22 g, 1.4 mmol), acetic acid (0.1 ml) and ethanol (5.2 ml) was heated under reflux for 6 hours. The
20 mixture was then made basic with aqueous sodium hydroxide and extracted with ethyl acetate. The organic phase was washed with water, dried over magnesium sulfate and concentrated. The residue was chromatographed on silica gel eluting with dichloromethane-methanol (99-1). After evaporation the residue was triturated with a small amount of ethyl acetate and crystallised. The solid was collected by filtration and
25 dried to give the title compound (80 mg) mp. : 170°C.

δ H(CDCI₃, 200MHz): 9.57 (1H, br), 8.79 (1H, s), 8.70 (1H, d), 8.51 (1H, d), 8.21 (1H, d), 8.15-7.98 (2H, m), 7.83-7.67 (2H, m), 7.15 (1H, d), 4.08 (3H, s), 3.35-3.06 (4H, m), 2.94 (2H, m), 2.48 (1H, tt), 2.48-1.80 (6H, m).

30 **Example 10 1-[2-(1-Oxo-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl)-ethyl]-piperidine-4-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide oxalate**



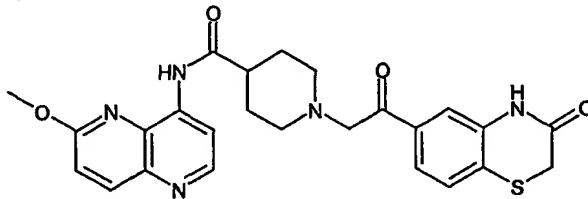
(a) 2-Allyl-2,3,4,5-tetrahydro-2-benzo(c)azepin-1-one

- A solution of the 2,3,4,5-tetrahydro-2-benzo(c)azepin-1-one (prepared by ring expansion of 1-tetralone as described by Grunewald et al. J. Het. Chem., 1994, 31, 1612) (6.8 g, 42 mmol) in N,N-dimethylformamide (100 ml) was added dropwise to a stirred solution of 60% sodium hydride (2.02 g, 51 mmol) in N,N-dimethylformamide (50 ml) at 0°C under argon. After stirring for 1 hour, allyl bromide (3.9 ml, 46 mmol) in N,N-dimethylformamide (20 ml) was added, and the mixture stirred at room temperature for 1.5 hours. The crude reaction mixture was then poured onto water and extracted with ethyl acetate. The organic layer was dried and evaporated to afford the title compound (10g).
- MS (+ve ion electrospray) m/z 202 (MH+).

- (b) (1-Oxo-1,3,4,5-tetrahydro-2-benzo(c)azepin-2-yl)-acetaldehyde
- A solution of the olefin (a) (8g, 40mmol) in dichloromethane (500 ml) was cooled to -78°C, and ozone bubbled through the solution for 2.5 hours until the solution turned a blue/grey colour. Excess ozone was removed by purging with argon, triethylamine (10 ml) added dropwise, and then the solution was allowed to warm to room temperature. It was washed with dilute aqueous hydrochloric acid, followed by water and brine, then dried and evaporated to afford the crude product. Chromatography on silica eluting with 20% ethyl acetate/hexane afforded an oil (2.8 g).
- MS (+ve ion electrospray) m/z 204 (MH+).

- (c) Title compound
- A solution of amine (1f) (115 mg, 0.4 mmol), aldehyde (b) (90 mg, 0.44 mmol) in chloroform/methanol (2.3 ml/0.3 ml) was treated with freshly activated 3Å molecular sieves and heated to reflux under argon for 8 hours. The cooled mixture was treated with sodium triacetoxyborohydride (130 mg, 0.6 mmol) and stirred for 16 hours at room temperature. The mixture was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate solution. The organic extract was dried and evaporated to give a brown oil. Chromatography on silica eluting with a methanol/ethyl acetate gradient afforded the free base of the title compound as an oil (60 mg, 32%).
- δ H (CDCl₃, 250MHz), 9.60 (1H, bs), 8.70 (1H, d), 8.50 (1H, d), 8.20 (1H, d), 7.65 (1H, dd), 7.40-7.30 (2H, m), 7.20-7.10 (2H, m), 4.05 (3H, s), 3.75 (2H, t), 3.25 (2H, t), 3.10 (2H, m), 2.85 (2H, t), 2.70 (2H, t), 2.50 (1H, m), 2.30-1.90 (8H, m)
- MS (+ve ion electrospray) m/z 474 (MH+).
- This was converted into the oxalate (45 mg) by dissolving the oil in chloroform (4 ml) and adding an equivalent of oxalic acid in ether (6 ml). The resulting solid was isolated by centrifugation and dried *in vacuo*.

Example 11 1-[2-Oxo-2-(3-oxo-3,4-dihydro-2*H*-benzo[1,4]thiazin-6-yl)-ethyl]-piperidine-4-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide oxalate



5 (a) 6-(2-Chloro-ethanoyl)-4*H*-benzo[1,4]thiazin-3-one

This was prepared by a modification of the procedure of Pesson and Techer (FR 1560628, 1969).

A solution of 3-oxo-3,4-dihydro-2*H*-benzo[1,4]thiazine (3g, 18 mmol) and chloroacetyl chloride (1.6 ml) in 1,2-dichloroethane (10 ml) was treated portionwise with
10 aluminium trichloride (5.3g, 39.9 mmol), while maintaining the internal temperature below 10°C with external cooling. After the addition was complete the mixture was heated to reflux for 1 hour, then allowed to recool to room temperature and added to a mixture of ice and concentrated aqueous hydrochloric acid (50g/20 ml). The resulting precipitate was filtered, dried and recrystallised from boiling ethanol affording a yellow
15 crystalline solid (1.87g, 42%).

MS (+ve ion electrospray) *m/z* 243 (MH⁺).

(b) Title compound

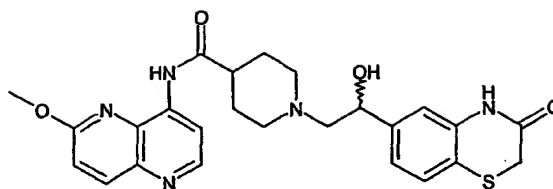
A mixture of piperidine (1f) (0.39g) and potassium carbonate (0.2g) in *N,N*-dimethylformamide (13 ml) was treated with (a) (0.33g). After 7 hours the mixture was
20 evaporated and the residue partitioned between ethyl acetate and saturated aqueous sodium bicarbonate solution. The organic extract was dried and evaporated to give a brown oil. Chromatography on silica eluting with a methanol/ethyl acetate gradient afforded the free base of the title compound as an oil (0.19g).

25 δ H(CDCI₃, 200MHz): 9.55 (1H, br), 8.72 (1H, d), 8.52 (1H, d), 8.20 (1H, d), 8.05 (1H, br), 7.70 (1H, d), 7.55 (1H, s), 7.40 (1H, d), 7.15 (1H, d), 4.10 (3H, s), 3.75 (2H, s), 3.45 (2H, s), 3.05 (2H, m), 2.40 (3H, m), 2.10 (4H, m).

MS (+ve ion electrospray) *m/z* 492 (MH⁺).

A portion of this material (20 mg) was converted to the title compound (20 mg) by
30 treating with oxalic acid in ether according to a similar procedure as for Example 10.

Example 12 R,S-1-[2-Hydroxy-2-(3-oxo-3,4-dihydro-2*H*-benzo[1,4]thiazin-6-yl)-ethyl]-piperidine-4-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide oxalate



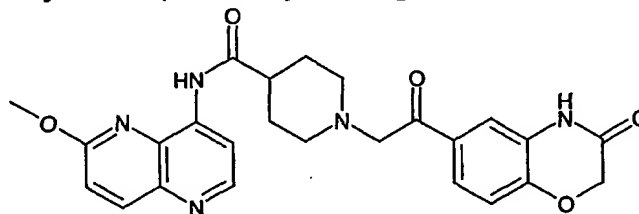
A mixture of Example 11 (0.15g, 0.3 mmol) and chloroform/methanol/water (10 ml/50 ml/10 ml) was treated with sodium borohydride (18 mg) and stirred vigorously overnight. The mixture was evaporated and the residue partitioned between ethyl acetate and saturated aqueous sodium bicarbonate solution. The organic extract was dried and evaporated to give a brown oil. Chromatography on silica eluting with a methanol/dichloromethane gradient afforded the free base of the title compound as a solid (0.025 g).

δ H(CDC1₃, 200MHz): 9.55 (1H, br), 8.70 (2H, m), 8.55 (1H, m), 8.25 (1H, d), 7.25 (1H, m), 7.15 (1H, d), 6.95 (2H, m), 4.72 (1H, dd), 4.10 (3H, s), 3.42 (2H, s), 2.95 (1H, m), 2.50 (4H, m), 2.20-1.90 (4H, m).

MS (+ve ion electrospray) m/z 494 (MH⁺).

This material (22 mg) was converted to the title compound (26 mg) by treating with oxalic acid in ether according to a similar procedure as for Example 10.

Example 13 1-[2-Oxo-2-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl)-ethyl]-piperidine-4-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide oxalate



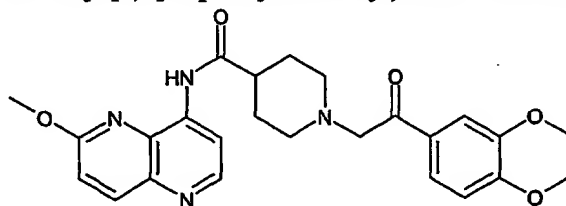
The free base of the title compound (61 mg) was prepared in 76% yield from piperidine (1f) and 6-(2-chloro-ethanoyl)-4H-benzo[1,4]oxazin-3-one by the same procedure as for Example 11(b).

δ H(d₆-DMSO, 200MHz): 9.30 (1H, br), 8.70 (1H, d), 8.40 (1H, d), 8.25 (1H, d), 7.70 (1H, dd), 7.60 (1H, d), 7.35 (1H, d), 7.05 (1H, d), 4.70 (2H, m), 4.12 (3H, s), 3.75 (2H, s), 3.00 (2H, m), 2.80 (1H, m), 2.25 (2H, m), 1.95 (2H, m), 1.80 (2H, m).

MS (+ve ion electrospray) m/z 476 (MH⁺).

This material was converted to the title compound (65 mg) by treating with oxalic acid in ether according to a similar procedure as for Example 10.

Example 14 1-[2-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-2-oxo-ethyl]-piperidine-4-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide oxalate



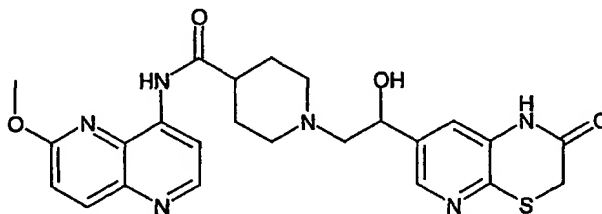
The free base of the title compound (0.21g) was prepared from piperidine (1f) and
 5 2-bromo-1-(2,3-dihydro-benzo[1,4]dioxin-6-yl)-ethanone in 43% yield according to the procedure of Example 11(b).

δ H(CDC13, 200MHz): 9.58 (1H, br), 8.70 (1H, d), 8.50 (1H, d), 8.20 (1H, d), 7.60 (2H, m), 7.15 (1H, d), 6.90 (1H, d), 4.35-4.25 (4H, m), 4.10 (3H, s), 3.75 (2H, s), 3.10 (2H, m), 2.50 (1H, m), 2.35(2H, m), 2.15-1.80 (6H, m).

10 MS (+ve ion electrospray) m/z 463 (MH⁺).

A portion of this material (20 mg) was converted to the title compound (25 mg) by treating with oxalic acid in ether according to a similar procedure as for Example 10.

Example 15 R and S-1-[2-Hydroxy-2-(2-oxo-2,3-dihydro-1H-pyrido[2,3-b][1,4]thiazin-7-yl)-ethyl]-piperidine-4-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide hydrochloride



(a) 6-Methoxycarbonylmethylsulfanyl-5-nitro-nicotinic acid methyl ester

20 A solution of 6-chloro-5-nitro-nicotinic acid methyl ester (1.0 g) [prepared as described by A.H. Berrie *et al. J. Chem. Soc.* 2590 –2594 (1951)] in dichloromethane (10 ml) containing triethylamine (0.76 ml) was treated with mercapto-acetic acid methyl ester (0.44 ml) and the solution was stirred at room temperature for 1 hour and evaporated to dryness. Sodium bicarbonate solution was added and the mixture was extracted with
 25 dichloromethane, dried (anhydrous sodium sulfate) and evaporated to afford a solid (1.0g).

MS (+ve ion electrospray) m/z 287 (MH⁺).

(b) 2-Oxo-2,3-dihydro-1H-pyrido[2,3-b][1,4]thiazine-7-carboxylic acid methyl ester

The ester (a) (1.0 g) in acetic acid (50 ml) was treated with iron powder (10 g) and the mixture was stirred and heated at 60°C for 1 hour, cooled and filtered. The filtrate was evaporated, treated with sodium bicarbonate solution and extracted with warm chloroform. It was dried over sodium sulfate and evaporated to give a white solid (0.85 g).

5 MS (+ve ion electrospray) m/z 225 (MH⁺).

(c) 2-Oxo-2,3-dihydro-1H-pyrido[2,3-b][1,4]thiazine-7-carboxylic acid

A solution of the ester (b) (2.8 g) in tetrahydrofuran (50 ml) was treated with 1M sodium hydroxide (30 ml). After 2 hours the mixture was concentrated to near dryness and acidified with 2M hydrochloric acid. Filtration and washing with water afforded a solid (2.5 g).

10 MS (-ve ion electrospray) m/z 209 (M-H⁻).

(d) 7-(2-Chloro-ethanoyl)-1H-pyrido[2,3-b][1,4]thiazin-2-one

A solution of acid (c) (1g) in tetrahydrofuran (60 ml) was treated with triethylamine (0.7 ml) then at 0°C with isobutylchloroformate (0.7 ml). After 0.5 hour the mixture was filtered and re-cooled to 0°C. A solution of excess diazomethane in ether was added, and the mixture stirred overnight at room temperature. Dichloromethane (20 ml) was added and the mixture was treated with 5M hydrochloric acid (10 ml). The mixture was stirred for 2 hours then partitioned between chloroform and saturated aqueous sodium bicarbonate solution. The organic extract was dried and evaporated affording an oil. Chromatography on silica eluting with an ethyl acetate/dichloromethane gradient afforded a solid (0.3g) comprising a 3:2 mixture of the desired product together with methyl 2-oxo-2,3-dihydro-1H-pyrido[2,3-b][1,4]thiazine-7-carboxylate.

20 MS (+ve ion electrospray) m/z 243 (MH⁺ of desired product)

25

(e) Title compound

A solution of amine (1f) (123 mg) in N,N-dimethylformamide (2 ml) was treated with potassium carbonate (60 mg) and the product mixture (d) (0.2g) at 0°C. After 3 hours water was added and the resulting precipitate was isolated by filtration. This material was suspended in methanol (70 ml) and treated with sodium borohydride (30 mg). After 2 hours the mixture was acidified with 2M hydrochloric acid and evaporated to dryness. The residue was partitioned between saturated aqueous sodium bicarbonate solution and chloroform. The organic extract was dried and evaporated. Chromatography on silica eluting with a 2-10% methanol in dichloromethane gradient afforded the free bases of the title compounds as a solid (0.14g).

30

35

δ H(CDCl₃, 200MHz): 9.55 (1H, br), 8.75 (1H, d), 8.55 (1H, d), 8.25 (1H, d), 8.15 (1H, d), 8.10 (1H, br), 7.25 (1H, d), 7.18 (1H, d), 4.80 (1H, dd), 4.15 (3H, s), 3.60 (2H, s), 3.25 (1H, m), 2.95 (1H, m), 2.60-2.40 (4H, m), 2.30-1.90 (5H, m).

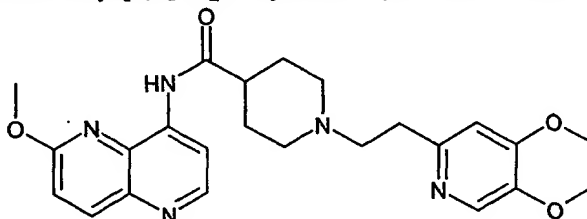
MS (+ve ion electrospray) m/z 495 (MH⁺).

- 5 A portion of this racemic material (80 mg) was subject to preparative hplc on a Chiralcell OD column (10 micron particle size) eluting with hexane/ethanol/ 50% aqueous hydroxylamine in a 50/50/0.1 v/v/v ratio. The sample was separated in 20 x 4 mg runs. The faster stereoisomer had a retention time of 13.8 minutes, the slower a retention time of 22.6 minutes. Around 30 mg of each stereoisomer were eventually isolated and each
- 10 isomer had an enantiomeric excess of >92%.

Each sample was dissolved in methanol /chloroform (3 ml/3 ml) and treated with a 1M solution of hydrochloric acid in ether (2 ml) then diluted with ether (5 ml). The resultant precipitates were isolated by centrifugation and dried *in vacuo* affording the title compounds (each ca 30 mg).

15

Example 16 1-[2-(2,3-Dihydro-[1,4]dioxino[2,3-c]pyridin-7-yl)-ethyl]-piperidine-4-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide hydrochloride



(a) 5-Benzyloxy-2-hydroxymethyl-1 *H*-pyridin-4-one

- 20 A mixture of 5-benzyloxy-2-hydroxymethyl-4-pyrone (prepared from Kojic acid by the method of D. Erol, J. Med. Chem., 1994, 29, 893) (9.7g, 40 mmol), concentrated aqueous (880) ammonia (100 ml), and ethanol (20 ml) was heated to reflux overnight. The mixture was allowed to cool to room temperature then filtered. The resultant solid was washed with ether and dried *in vacuo* (5.9g).

25 MS (+ve ion electrospray) m/z 232 (MH⁺).

(b) (2,3-Dihydro-[1,4]dioxino[2,3-c]pyridin-7-yl)-methanol

- A solution of (a) (2g, 8.7 mmol) in water (220 ml) containing sodium hydroxide (17 mmol) was hydrogenated over 10% palladium on charcoal (1g) for 4 hours. The mixture was filtered and evaporated to give a white solid. This solid was dissolved in
- 30 N,N-dimethylformamide (8 ml) then treated with potassium carbonate (2.9g) and 1,2-dibromoethane (0.6 ml, 7 mmol). The mixture was heated at 85°C overnight. The cooled

mixture was evaporated onto silica and chromatographed eluting with 10-30% methanol in ethyl acetate affording a white solid (250 mg, 21 %).

MS (+ve ion electrospray) m/z 232 (MH+).

5 (c) 2,3-Dihydro-[1,4]dioxino[2,3-c]pyridine-7-carboxaldehyde

A solution of (b) (250 mg, 1.5 mmol) in dichloromethane (5 ml) was treated with manganese dioxide (650 mg, 7.5 mmol). After 3 days the mixture was filtered and evaporated affording a white solid (150 mg, 61%).

MS (+ve ion electrospray) m/z 166 (MH+).

10

(d) 1-(2,3-Dihydro-[1,4]dioxino[2,3-c]pyridin-7-yl)-2-trimethylsilyl-ethanol

A solution of aldehyde (c) (1.2g) in tetrahydrofuran (20 ml) was treated at 0°C under argon with a solution of trimethylsilylmethylmagnesium chloride in ether (1M; 8 ml, 8 mmol). After 2 hours the mixture was partitioned between ether - half saturated aqueous ammonium chloride solution. The organic extract was dried and evaporated

15

affording an oil (1.6g).

MS (+ve ion electrospray) m/z 254 (MH+).

(e) 7-Vinyl-2,3-dihydro-[1,4]dioxino[2,3-c]pyridine

20

A solution of (d) (1.6g) in tetrahydrofuran (20 ml) was treated at 0°C under argon with a solution of potassium t-butoxide in tetrahydrofuran (1M; 7.6 ml, 7.6 mmol). After 2 hours the mixture was partitioned between ethyl acetate - half saturated aqueous ammonium chloride solution. The organic extract was dried and evaporated affording an oil (1.5g).

25

MS (+ve ion electrospray) m/z 164 (MH+).

(f) Title compound

30

A mixture of olefin (e) (65 mg) and amine (1f) (115 mg) in ethanol (1 ml) containing acetic acid (25 mg) was heated to reflux for 3 days. The mixture was partitioned between ethyl acetate and 1M sodium hydroxide solution. The organic extract was dried and evaporated affording an oil (0.2g). Chromatography on silica eluting with a 0-20% methanol in ethyl acetate gradient afforded the free base of the title compound as a solid (36 mg).

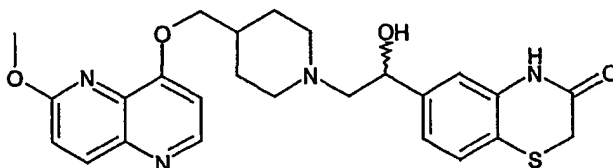
35

δ H(CD₃OD, 200MHz): 8.62 (1H, d), 8.50 (1H, d), 8.20 (1H, d) 8.00 (1H, s), 7.25 (1H, d), 6.88 (1H, s), 4.36 (2H, m), 4.30 (2H, m), 4.15 (3H, s), 2.82 (1H, m), 2.55 (2H, m), 2.20-2.00 (4H, m), 1.45-1.25 (4H, m), 1.90 (2H, m).

MS (+ve ion electrospray) m/z 450 (MH+).

This was converted to the hydrochloride salt (42 mg) by the method of Example 15.

Example 17 R,S-6-{1-Hydroxy-2-[4-(6-methoxy-[1,5]naphthyridin-4-yloxymethyl)-piperidin-1-yl]-ethyl}-4H-benzo[1,4]thiazin-3-one hydrochloride



5

(a) 4-(6-Methoxy-[1,5]naphthyridin-4-yloxymethyl)-piperidine-1-carboxylic acid *tert*-butyl ester

4-Hydroxymethyl-piperidine-1-carboxylic acid *tert*-butyl ester (610 mg) was added to a stirred suspension of sodium hydride (120 mg of a 60% dispersion in mineral oil) in N,N-dimethylformamide (6 ml) at 0°C under argon. After 1 hour triflate (1b) (924 mg) was added and the mixture was heated at 95°C overnight. The mixture was partitioned between ethyl acetate and water. The organic extract was washed with brine then dried and evaporated affording an oil (1 g). Chromatography on silica eluting with a 0-100% ethyl acetate in dichloromethane gradient afforded an oil (0.54g, 48%).

MS (+ve ion electrospray) m/z 374 (MH+).

15

(b) 2-Methoxy-8-(piperidin-4-ylmethoxy)-[1,5]naphthyridine

A solution of carbamate (a) (0.95g) in dichloromethane/trifluoroacetic acid (20 ml/20 ml) was stirred for 1 hour then evaporated to dryness, azeotroping with toluene and chloroform. The residue was dissolved in water and extracted with ethyl acetate. The aqueous extract was basified with solid potassium carbonate and evaporated. The residue stirred with 10% methanol in chloroform. Filtration and evaporation afforded an oil (0.7g).

MS (+ve ion electrospray) m/z 274 (MH+).

25

(c) 6-{2-[4-(6-Methoxy-[1,5]naphthyridin-4-yloxymethyl)-piperidin-1-yl]-ethanoyl}-4H-benzo[1,4]thiazin-3-one

A solution of amine (b) (0.4g) in N,N-dimethylformamide (5 ml) was treated with potassium carbonate (0.3g) then chloromethylketone (11a) (0.36g). The mixture was stirred overnight then filtered and concentrated to around 2 ml of N,N-dimethylformamide. Water (ca 5 ml) was added dropwise, and the resulting yellow solid was isolated by filtration and dried *in vacuo* (0.5g, 73%).

MS (+ve ion electrospray) m/z 479 (MH+).

30

(d) Title compound

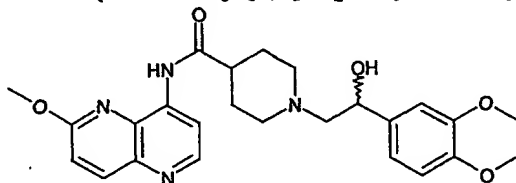
A solution of ketone (c) (0.5g) in methanol/chloroform (180 ml/22 ml) was treated with sodium borohydride (0.15g). After 1 hour the mixture was acidified with 5M hydrochloric acid then basified with saturated aqueous sodium bicarbonate solution. The mixture was concentrated then extracted with ethyl acetate. The organic extract was washed with brine then dried and evaporated affording an oil. Chromatography on silica eluting with a 0-5% methanol in ethyl acetate gradient afforded a white solid (0.3g, 63%).

δ H(CDCl₃, 200MHz): 9.85 (1H, br), 8.60 (1H, d), 8.18 (1H, d), 7.28 (1H, m), 7.12 (1H, d), 7.02-6.95 (2H, m), 6.90 (1H, d), 4.70 (1H, dd), 4.10 (5H, m), 3.40 (2H, s), 3.25 (1H, m), 2.90 (1H, m), 2.50 (1H, m), 2.40 (2H, m), 2.20-2.00 (4H, m), 1.60 (2H, m)

MS (+ve ion electrospray) m/z 481 (MH⁺).

This was converted to the hydrochloride salt by the procedure of Example 15.

Example 18 R,S-1-[2-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-2-hydroxy-ethyl]-piperidine-4-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide oxalate



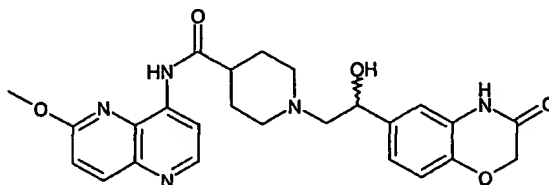
This was prepared from Example 14 by reduction with sodium borohydride by the method of Example (17d).

δ H(CDCl₃, 200MHz): 9.60 (1H, br), 8.70 (1H, d), 8.52 (1H, d), 8.25 (1H, d), 7.20 (1H, d), 6.90-6.80 (3H, m), 4.70 (1H, dd), 4.25 (4H, s), 4.10 (3H, s), 3.30 (1H, m), 3.00 (1H, m), 2.60-2.40 (5H, m), 2.30-1.90 (4H, m).

MS (+ve ion electrospray) m/z 481 (MH⁺).

This was converted to the oxalate salt (10 mg) by the procedure of Example 15.

Example 19 R,S-1-[2-Hydroxy-2-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl)-ethyl]-piperidine-4-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide oxalate



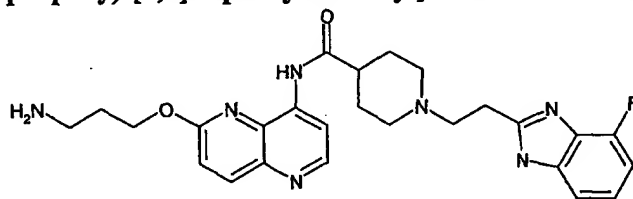
The free base of the title compound was prepared from Example 13 by reduction with sodium borohydride by the method of Example (17d) but the reaction was for 1 hour and without chloroform as the co-solvent.

δ H(d-6 DMSO, 200MHz): 9.77 (1H, br), 8.68 (1H, d), 8.40 (1H, d), 8.30 (1H, d), 7.30 (1H, d), 6.95-6.88 (3H, m), 5.00 (1H, br), 4.66 (1H, m), 4.55 (2H, s), 4.15 (3H, s), 3.00 (2H, m), 2.70 (1H, m), 2.50-2.35 (2H, m), 2.20-2.10 (2H, m), 2.00-1.90 (2H, m), 1.85-1.65 (2H, m).

MS (+ve ion electrospray) m/z 478 (MH⁺).

This material was converted to the title compound (44 mg) by treating with oxalic acid in ether according to a similar procedure as for Example 10.

Example 20 1-[2-(4-Fluoro-1H-benzoimidazol-2-yl)-ethyl]-piperidine-4-carboxylic acid [6-(3-amino-propoxy)-[1,5]naphthyridin-4-yl]-amide bis-trifluoroacetate



(a) 8-Amino-1-H-[1,5]naphthyridin-2-one hydrobromide

A suspension of amine (1c) (4.20g, 24 mmol) in concentrated hydrobromic acid (35 ml) was heated at 120°C for 2 hours. The mixture was set aside in the refrigerator for 2 hours, then filtered, washing with small amounts of cold water then diethyl ether.

Drying *in vacuo* afforded the product as a white solid (6.1g, 100%).

MS (+ve ion electrospray) m/z 162 (MH⁺).

(b) [3-(8-Amino-[1,5]naphthyridin-2-yloxy)-propyl]-carbamic acid tert-butyl ester

A suspension of hydrobromide salt (a) (1.2g, 5 mmol) in N,N-dimethylformamide (10 ml) at 40°C was treated with potassium carbonate (2.1g, 15 mmol) then after 0.25 hours with a solution of (3-bromo-propyl)-carbamic acid *tert*-butyl ester (2g, 7.4 mmol) in N,N-dimethylformamide (5 ml). The mixture was heated for 4 hours at 40°C, then evaporated to dryness. The residue was partitioned between ethyl acetate and dilute aqueous sodium chloride solution. The organic extract was dried and evaporated to give a brown oil (2.2g). This was chromatographed on silica eluting with a methanol/ethyl

acetate gradient affording the product as a clear oil (1.0g).

MS (+ve ion electrospray) m/z 319 (MH⁺).

(c) (3-{8-[(1-{1-[2-(4-Fluoro-1H-benzoimidazol-2-yl)-ethyl]-piperidin-4-yl}-methanoyl)-amino]-[1,5]naphthyridin-2-yloxy}-propyl)-carbamic acid tert-butyl ester

This was prepared from amine (b) and acid (4c) in 42% yield according to the procedure for Example (4d) affording an oil (0.31g).

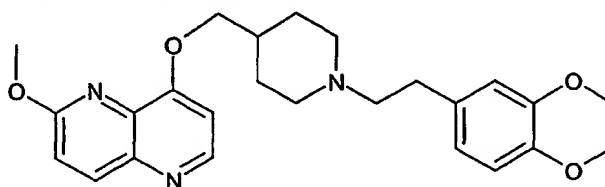
MS (+ve ion electrospray) m/z 592 (MH⁺).

5 (d) Title compound

The carbamate (c) (0.20g) was treated with trifluoroacetic acid (20 ml). After 2 hours the mixture was evaporated and the residue triturated with chloroform, affording the title compound as a white solid (0.13g).

10 δ H(d-6 DMSO, 200MHz): 10.00 (1H, br), 8.80 (1H, d), 8.50 (1H, d), 8.35 (1H, d), 7.80 (3H, br), 7.15 (1H, m), 7.00 (1H, m), 4.70 (2H, t), 3.90-2.90 (11H, m), 2.20-1.80 (6H, m)
MS (+ve ion electrospray) m/z 492 (MH⁺).

Example 21 8-{1-[2-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-ethyl]-piperidin-4-ylmethoxy}-2-methoxy-[1,5]naphthyridine hydrochloride



15

(a) 6-(2-Chloro-ethyl)-2,3-dihydro-benzo[1,4]dioxine

A solution of 2-chloro-1-(2,3-dihydro-benzo[1,4]dioxin-6-yl)-ethanone (0.5g) in trifluoroacetic acid/triethylsilane (4 ml/1.3 ml) was stirred overnight then partitioned between dichloromethane and dilute aqueous sodium bicarbonate solution. The organic
20 extract was dried and evaporated to give a brown oil (0.42g) This was chromatographed on silica eluting with a dichloromethane/petroleum ether gradient affording the product as a clear oil (0.23g).

MS (+ve ion electrospray) m/z 199 (MH⁺).

25 (b) 6-(2-Iodo-ethyl)-2,3-dihydro-benzo[1,4]dioxine

A solution of (a) (0.22g) in acetone (10 ml) was treated with sodium iodide (0.6g) and heated to reflux overnight. The mixture was filtered and evaporated. The residue was partitioned between dichloromethane and dilute aqueous sodium sulphite solution. The organic extract was dried and evaporated to give a brown oil (0.25g) .

30 MS (+ve ion electrospray) m/z 291 (MH⁺).

(c) Title compound

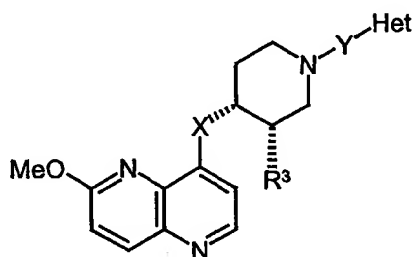
This was prepared from Example (17b) (0.17g) and Example (21b) (0.2g) following the procedure for Example (1j) affording after chromatography the free base of the title compound as an oil (0.12g).

δ H(CD₃OD, 200MHz): 8.50 (1H, d), 8.10 (1H, d), 7.20 (1H, d), 7.15 (1H, d), 6.75-6.60 (3H, m), 4.20 (4H, s), 4.15 (1H, d), 4.07 (3H, s), 3.10 (2H, m), 2.70 (2H, m), 2.55 (2H, m), 2.15 (2H, m), 2.00 (2H, m), 1.45 (2H, m).

MS (+ve ion electrospray) m/z 436 (MH⁺).

This was converted to the hydrochloride salt (0.13g) by the procedure of Example 15.

10 The following compounds were prepared by procedures analogous to those described herein:



Example	Name	X	R ³	Y	Het	Preparation
22	6-{2-[4-(6-Methoxy-[1,5]naphthyridin-4-yloxymethyl)-piperidin-1-yl]-ethyl}-4H-benzo[1,4]thiazin-3-one	OCH ₂	H	CH ₂ CH ₂		Alkylation of amine (17b) with (1i) according to the procedure of Example (1j).
23	[(3R,4S)-4-[(6-Methoxy-[1,5]naphthyridin-4-ylcarbonyl)-methyl]-1-(3-oxo-3,4-dihydro-2H-benzo[1,4]thiazin-6-ylmethyl)-piperidin-3-yl]-acetic acid trifluoroacetate salt	NHCOCH ₂	CH ₂ CO ₂ H	CH ₂		Reaction of (3R,4S)-3-tert-butoxycarbonylmethyl-4-carboxymethyl-piperidine-1-carboxylic acid benzyl ester (prepared from ((3R,4S)-3-vinyl-piperidin-4-yl)-acetic acid methyl ester by methods described in WO 00343383) with (1c) by the method of Example (1e) followed by hydrogenation (Pd/C) and reaction with 3-oxo-3,4-dihydro-2H-benzo[1,4]thiazine-6-carbaldehyde and triacetoxyborohydride, followed by deprotection with TFA.

Biological Activity

The MIC ($\mu\text{g/ml}$) of test compounds against various organisms was determined: *S. aureus* Oxford, *S. aureus* WCUH29, *S. pneumoniae* 1629, *S. pneumoniae* N1387, *S. pneumoniae* ERY 2, *E. faecalis* I, *E. faecalis* 7, *H. influenzae* Q1, *H. influenzae* NEMC1, 5 *M. catarrhalis* 1502.

Examples 1-4, 12, 13, 15, 16, 18 had MIC values $\leq 4\mu\text{g/ml}$ versus all these organisms.

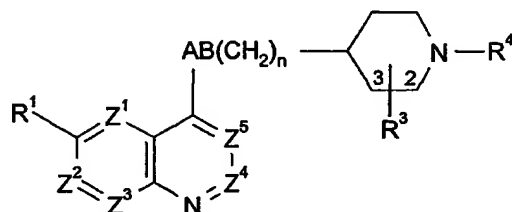
Examples 7, 14, 17, 19, 22 had MIC values $\leq 16\mu\text{g/ml}$ versus all these organisms.

Examples 5,6, 9,11, 21, 22 had MIC values $\leq 64\mu\text{g/ml}$ versus all these organisms.

Other examples had MIC values less than $64\mu\text{g/ml}$ versus at least one of these organisms.

Claims

1. A compound of formula (I) or a pharmaceutically acceptable derivative thereof:



5

(I)

wherein:

one of Z¹, Z², Z³, Z⁴ and Z⁵ is N, one is CR^{1a} and the remainder are CH, or one of Z¹,
 10 Z², Z³, Z⁴ and Z⁵ is CR^{1a} and the remainder are CH;

R¹ and R^{1a} are independently selected from hydrogen; hydroxy; (C₁₋₆) alkoxy optionally
 substituted by (C₁₋₆)alkoxy, amino, piperidyl, guanidino or amidino any of which is
 optionally N-substituted by one or two (C₁₋₆)alkyl, acyl or (C₁₋₆)alkylsulphonyl groups,
 15 CONH₂, hydroxy, (C₁₋₆)alkylthio, heterocyclylthio, heterocyclyloxy, arylthio, aryloxy,
 acylthio, acyloxy or (C₁₋₆)alkylsulphonyloxy; (C₁₋₆)alkoxy-substituted (C₁₋₆)alkyl;
 halogen; (C₁₋₆)alkyl; (C₁₋₆)alkylthio; trifluoromethyl; nitro; azido; acyl; acyloxy;
 acylthio; (C₁₋₆)alkylsulphonyl; (C₁₋₆)alkylsulphoxide; arylsulphonyl; arylsulphoxide or
 an amino, piperidyl, guanidino or amidino group optionally N-substituted by one or two
 20 (C₁₋₆)alkyl, acyl or (C₁₋₆)alkylsulphonyl groups,
 or when Z¹ is CR^{1a}, R¹ and R^{1a} may together represent (C₁₋₂)alkylenedioxy,
 provided that when Z¹, Z², Z³, Z⁴ and Z⁵ are CR^{1a} or CH, then R¹ is not hydrogen;

R³ is hydrogen; or

25 R³ is in the 2- or 3-position and is:

carboxy; (C₁₋₆)alkoxycarbonyl; aminocarbonyl wherein the amino group is optionally
 substituted by hydroxy, (C₁₋₆)alkyl, hydroxy(C₁₋₆)alkyl, aminocarbonyl(C₁₋₆)alkyl, (C₂₋₆)
 alkenyl, (C₁₋₆)alkylsulphonyl, trifluoromethylsulphonyl, (C₂₋₆)alkenylsulphonyl, (C₁₋₆)
 alkoxy, (C₁₋₆)alkylcarbonyl, (C₂₋₆)alkenyloxycarbonyl or (C₂₋₆)
 30 alkenylcarbonyl and optionally further substituted by (C₁₋₆)alkyl, hydroxy(C₁₋₆)alkyl,
 aminocarbonyl(C₁₋₆)alkyl or (C₂₋₆)alkenyl; cyano; tetrazolyl; 2-oxo-oxazolidinyl
 optionally substituted by R¹⁰; 3-hydroxy-3-cyclobutene-1,2-dione-4-yl; 2,4-

thiazolidinedione-5-yl; tetrazol-5-ylaminocarbonyl; 1,2,4-triazol-5-yl optionally substituted by R¹⁰; or 5-oxo-1,2,4-oxadiazol-3-yl; or

- (C₁₋₄)alkyl or ethenyl optionally substituted with any of the groups listed above for R³
 5 and/or 0 to 2 groups R¹² independently selected from:
 halogen; (C₁₋₆)alkylthio; trifluoromethyl; (C₁₋₆)alkoxycarbonyl; (C₁₋₆)alkylcarbonyl; (C₂₋₆)alkenyloxycarbonyl; (C₂₋₆)alkenylcarbonyl; hydroxy optionally substituted by (C₁₋₆)alkyl, (C₂₋₆)alkenyl, (C₁₋₆)alkoxycarbonyl, (C₁₋₆)alkylcarbonyl, (C₂₋₆)alkenyloxycarbonyl, (C₂₋₆)alkenylcarbonyl or aminocarbonyl wherein the amino
 10 group is optionally substituted by (C₁₋₆)alkyl, (C₂₋₆)alkenyl, (C₁₋₆)alkylcarbonyl or (C₂₋₆)alkenylcarbonyl; amino optionally mono- or disubstituted by (C₁₋₆)alkoxycarbonyl, (C₁₋₆)alkylcarbonyl, (C₂₋₆)alkenyloxycarbonyl, (C₂₋₆)alkenylcarbonyl, (C₁₋₆)alkyl, (C₂₋₆)alkenyl, (C₁₋₆)alkylsulphonyl, (C₂₋₆)alkenylsulphonyl or aminocarbonyl wherein the amino group is optionally substituted by (C₁₋₆)alkyl or (C₂₋₆)alkenyl; aminocarbonyl
 15 wherein the amino group is optionally substituted by (C₁₋₆)alkyl, hydroxy(C₁₋₆)alkyl, aminocarbonyl(C₁₋₆)alkyl, (C₂₋₆)alkenyl, (C₁₋₆)alkoxycarbonyl, (C₁₋₆)alkylcarbonyl, (C₂₋₆)alkenyloxycarbonyl or (C₂₋₆)alkenylcarbonyl and optionally further substituted by (C₁₋₆)alkyl, hydroxy(C₁₋₆)alkyl, aminocarbonyl(C₁₋₆)alkyl or (C₂₋₆)alkenyl; oxo; (C₁₋₆)alkylsulphonyl; (C₂₋₆)alkenylsulphonyl; or (C₁₋₆)aminosulphonyl wherein the amino
 20 group is optionally substituted by (C₁₋₆)alkyl or (C₂₋₆)alkenyl; or

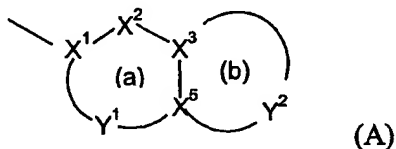
- when R³ is in the 3-position it may instead be selected from hydroxy optionally substituted by (C₁₋₆)alkyl, (C₂₋₆)alkenyl, (C₁₋₆)alkoxycarbonyl, (C₁₋₆)alkylcarbonyl, (C₂₋₆)alkenyloxycarbonyl, (C₂₋₆)alkenylcarbonyl or aminocarbonyl wherein the amino
 25 group is optionally substituted by (C₁₋₆)alkyl, (C₂₋₆)alkenyl, (C₁₋₆)alkylcarbonyl or (C₂₋₆)alkenylcarbonyl, and amino optionally mono- or disubstituted by (C₁₋₆)alkoxycarbonyl, (C₁₋₆)alkylcarbonyl, (C₂₋₆)alkenyloxycarbonyl, (C₂₋₆)alkenylcarbonyl, (C₁₋₆)alkyl, (C₂₋₆)alkenyl, (C₁₋₆)alkylsulphonyl, (C₂₋₆)alkenylsulphonyl or aminocarbonyl wherein the amino group is optionally substituted by (C₁₋₆)alkyl or (C₂₋₆)alkenyl;

- 30 in addition when R³ is disubstituted with a hydroxy or amino containing substituent and a carboxy containing substituent these may optionally together form a cyclic ester or amide linkage, respectively;

- 35 R¹⁰ is selected from (C₁₋₄)alkyl; (C₂₋₄)alkenyl and aryl any of which may be optionally substituted by a group R¹² as defined above; carboxy; aminocarbonyl wherein the amino group is optionally substituted by hydroxy, (C₁₋₆)alkyl, (C₂₋₆)alkenyl, (C₁₋

- 6)alkylsulphonyl, trifluoromethylsulphonyl, (C₂₋₆)alkenylsulphonyl, (C₁₋₆)alkoxycarbonyl, (C₁₋₆)alkylcarbonyl, (C₂₋₆)alkenyloxycarbonyl or (C₂₋₆)alkenylcarbonyl and optionally further substituted by (C₁₋₆)alkyl or (C₂₋₆)alkenyl; (C₁₋₆)alkylsulphonyl; trifluoromethylsulphonyl; (C₂₋₆)alkenylsulphonyl; (C₁₋₆)alkoxycarbonyl; (C₁₋₆)alkylcarbonyl; (C₂₋₆)alkenyloxycarbonyl; and (C₂₋₆)alkenylcarbonyl;

R⁴ is a group -U-V-R⁵ where R⁵ is an optionally substituted bicyclic carbocyclic or heterocyclic ring system (A):



10

containing up to four heteroatoms in each ring in which
at least one of rings (a) and (b) is aromatic;

X¹ is C or N when part of an aromatic ring or CR¹⁴ or N when part of a non aromatic ring;

- 15 X² is N, NR¹³, O, S(O)_x, CO or CR¹⁴ when part of an aromatic or non-aromatic ring or may in addition be CR¹⁴R¹⁵ when part of a non aromatic ring;

X³ and X⁵ are independently N or C;

- Y¹ is a 0 to 4 atom linker group each atom of which is independently selected from N, NR¹³, O, S(O)_x, CO and CR¹⁴ when part of an aromatic or non-aromatic ring or
20 may additionally be CR¹⁴R¹⁵ when part of a non aromatic ring,

Y² is a 2 to 6 atom linker group, each atom of Y² being independently selected from N, NR¹³, O, S(O)_x, CO and CR¹⁴ when part of an aromatic or non-aromatic ring or may additionally be CR¹⁴R¹⁵ when part of a non aromatic ring;

each of R¹⁴ and R¹⁵ is independently selected from: H; (C₁₋₄)alkylthio; halo;

- 25 carboxy(C₁₋₄)alkyl; halo(C₁₋₄)alkoxy; halo(C₁₋₄)alkyl; (C₁₋₄)alkyl; (C₂₋₄)alkenyl; (C₁₋₄)alkoxycarbonyl; formyl; (C₁₋₄)alkylcarbonyl; (C₂₋₄)alkenyloxycarbonyl; (C₂₋₄)alkenylcarbonyl; (C₁₋₄)alkylcarbonyloxy; (C₁₋₄)alkoxycarbonyl(C₁₋₄)alkyl; hydroxy; hydroxy(C₁₋₄)alkyl; mercapto(C₁₋₄)alkyl; (C₁₋₄)alkoxy; nitro; cyano; carboxy; amino or aminocarbonyl optionally substituted as for corresponding substituents in R³; (C₁₋₄)alkylsulphonyl; (C₂₋₄)alkenylsulphonyl; or aminosulphonyl wherein the amino group is
30 optionally substituted by (C₁₋₄)alkyl or (C₂₋₄)alkenyl; aryl; aryl(C₁₋₄)alkyl; aryl(C₁₋₄)alkoxy;

each R¹³ is independently hydrogen, trifluoromethyl; (C₁₋₄)alkyl optionally substituted by hydroxy, carboxy, (C₁₋₆)alkoxycarbonyl, (C₁₋₆)alkoxy, (C₁₋₆)alkylthio, halo or trifluoromethyl; (C₂₋₄)alkenyl; aryl; aryl (C₁₋₄)alkyl; arylcarbonyl;

35

heteroarylcarbonyl; (C₁₋₄)alkoxycarbonyl; (C₁₋₄)alkylcarbonyl; formyl; (C₁₋₆)alkylsulphonyl; or aminocarbonyl wherein the amino group is optionally substituted by (C₁₋₄)alkoxycarbonyl, (C₁₋₄)alkylcarbonyl, (C₂₋₄)alkenyloxycarbonyl, (C₂₋₄)alkenylcarbonyl, (C₁₋₄)alkyl or (C₂₋₄)alkenyl and optionally further substituted by (C₁₋₄)alkyl or (C₂₋₄)alkenyl;

each x is independently 0, 1 or 2;

U is CO, SO₂ or CH₂ and V is CR¹⁷R¹⁸ or U is CH₂ and V is CO, SO₂ or CR¹⁷R¹⁸;

R¹⁷ and R¹⁸ are independently selected from hydrogen, hydroxy optionally substituted by (C₁₋₆)alkyl, (C₂₋₆)alkenyl, (C₁₋₆)alkoxycarbonyl, (C₁₋₆)alkylcarbonyl, (C₂₋₆)alkenyloxycarbonyl, (C₂₋₆)alkenylcarbonyl or aminocarbonyl wherein the amino group is optionally substituted by (C₁₋₆)alkyl, (C₂₋₆)alkenyl, (C₁₋₆)alkylcarbonyl or (C₂₋₆)alkenylcarbonyl; and amino optionally mono- or disubstituted by (C₁₋₆)alkoxycarbonyl, (C₁₋₆)alkylcarbonyl, (C₂₋₆)alkenyloxycarbonyl, (C₂₋₆)alkenylcarbonyl, (C₁₋₆)alkyl, (C₂₋₆)alkenyl, (C₁₋₆)alkylsulphonyl, (C₂₋₆)alkenylsulphonyl or aminocarbonyl wherein the amino group is optionally substituted by (C₁₋₆)alkyl or (C₂₋₆)alkenyl;

n is 0 or 1 and AB is NR¹¹CO, CONR¹¹, CO-CR⁸R⁹, CR⁶R⁷-CO, O-CR⁸R⁹, CR⁶R⁷-O, NHR¹¹-CR⁸R⁹, CR⁶R⁷-NHR¹¹, NR¹¹SO₂, CR⁶R⁷-SO₂ or CR⁶R⁷-CR⁸R⁹;
or n is 0 or 1 and AB is NH-CO-NH or NH-CO-O;
or n is 0 and AB is CR⁶R⁷SO₂NR¹¹, CR⁶R⁷CONR¹¹ or CR⁶R⁷CH₂NR¹¹;
provided that R⁶ and R⁷, and R⁸ and R⁹ are not both optionally substituted hydroxy or amino;

and wherein:
each of R⁶, R⁷, R⁸ and R⁹ is independently selected from: H; (C₁₋₆)alkoxy; (C₁₋₆)alkylthio; halo; trifluoromethyl; azido; (C₁₋₆)alkyl; (C₂₋₆)alkenyl; (C₁₋₆)alkoxycarbonyl; (C₁₋₆)alkylcarbonyl; (C₂₋₆)alkenyloxycarbonyl; (C₂₋₆)alkenylcarbonyl; hydroxy, amino or aminocarbonyl optionally substituted as for corresponding substituents in R³; (C₁₋₆)alkylsulphonyl; (C₂₋₆)alkenylsulphonyl; or (C₁₋₆)aminosulphonyl wherein the amino group is optionally substituted by (C₁₋₆)alkyl or (C₂₋₆)alkenyl;
or R⁶ and R⁸ together represent a bond and R⁷ and R⁹ are as above defined;

and each R¹¹ is independently H; trifluoromethyl; (C₁₋₆)alkyl; (C₂₋₆)alkenyl; (C₁₋₆)alkoxycarbonyl; (C₁₋₆)alkylcarbonyl; or aminocarbonyl wherein the amino group is optionally substituted by (C₁₋₆)alkoxycarbonyl, (C₁₋₆)alkylcarbonyl, (C₂₋

6)alkenyloxycarbonyl, (C₂₋₆)alkenylcarbonyl, (C₁₋₆)alkyl or (C₂₋₆)alkenyl and optionally further substituted by (C₁₋₆)alkyl or (C₂₋₆)alkenyl;

or where one of R³ and R⁶, R⁷, R⁸ or R⁹ contains a carboxy group and the other contains a hydroxy or amino group they may together form a cyclic ester or amide linkage.

2. A compound according to claim 1 wherein Z⁵ is CH or N, Z³ is CH or CF and Z¹, Z² and Z⁴ are each CH, or Z¹ is N, Z³ is CH or CF and Z², Z⁴ and Z⁵ are each CH.

3. A compound according to any preceding claim wherein R¹ is methoxy and R^{1a} is H or when Z³ is CR^{1a} it may be C-F.

4. A compound according to any preceding claim wherein R³ is hydrogen or hydroxy.

5. A compound according to any preceding claim wherein n is 0 and either A is CHOH or CH₂ and B is CH₂ or A is NH and B is CO.

6. A compound according to any preceding claim wherein the group -U-V- is - (CH₂)₂-, CH₂CH(OH) or CH₂CO

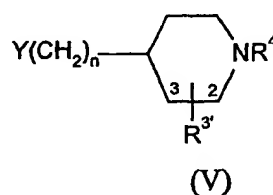
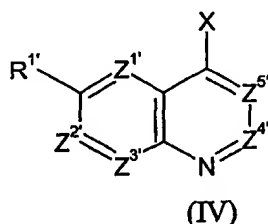
7. A compound according to any preceding claim wherein the heterocyclic ring (A) has ring (a) aromatic selected from optionally substituted benzo and pyrido and ring (b) non-aromatic in which preferably Y² has 3-5 atoms including NR¹³, where R¹³ is other than hydrogen, O or S bonded to X⁵ and NHCO bonded via N to X³, or O bonded to X³; or ring (a) is aromatic and (b) is aromatic in which preferably Y² contains 2-3 heteroatoms, one of which is S and 1-2 are N, with one N bonded to X³.

8. A compound according to any of claims 1 to 6 wherein R⁵ is selected from: 4H-benzo[1,4]thiazin-3-one-6-yl (3-oxo-3,4-dihydro-2H-benzo[1,4]thiazin-6-yl)
benzo[1,3]dioxol-5-yl
2,3-Dihydro-benzo[1,4]dioxin-6-yl
4-fluorobenzimidazol-2-yl
benzo[1,2,5]thiadiazol-5-yl
quinoxalin-2-yl
2-oxo-2,3-dihydro-1H-pyrido[2,3-b][1,4]thiazin-7-yl
2,3-dihydro-[1,4]dioxino[2,3-c]pyridin-7-yl.

9. A compound selected from:
- 1-[2-(3-Oxo-3,4-dihydro-2*H*-benzo[1,4]thiazin-6-yl)-ethyl]-piperidine-4-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide
- 1-(2-Benzo[1,3]dioxol-5-yl-ethyl)-piperidine-4-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide
- 5 1-[2-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-ethyl]-piperidine-4-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide
- 1-[2-(4-Fluoro-1*H*-benzoimidazol-2-yl)-ethyl]-piperidine-4-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide
- 10 1-(2-Benzo[1,2,5]thiadiazol-5-yl-ethyl)-piperidine-4-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide
- 1-[2-(3-Methyl-2-oxo-2,3-dihydro-benzooxazol-6-yl)-ethyl]-piperidine-4-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide
- 1-[2-(3-Oxo-3,4-dihydro-2*H*-benzo[1,4]oxazin-6-yl)-ethyl]-piperidine-4-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide
- 15 1-[2-(2-Oxo-2,3-dihydro-benzooxazol-5-yl)-ethyl]-piperidine-4-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide
- 1-(2-Quinoxalin-2-yl-ethyl)-piperidine-4-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide
- 20 1-[2-(1-Oxo-1,3,4,5-tetrahydro-benzo[*c*]azepin-2-yl)-ethyl]-piperidine-4-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide
- 1-[2-Oxo-2-(3-oxo-3,4-dihydro-2*H*-benzo[1,4]thiazin-6-yl)-ethyl]-piperidine-4-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide
- R,S-1-[2-Hydroxy-2-(3-oxo-3,4-dihydro-2*H*-benzo[1,4]thiazin-6-yl)-ethyl]-piperidine-4-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide
- 25 1-[2-Oxo-2-(3-oxo-3,4-dihydro-2*H*-benzo[1,4]oxazin-6-yl)-ethyl]-piperidine-4-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide
- 1-[2-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-2-oxo-ethyl]-piperidine-4-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide
- 30 R and S-1-[2-Hydroxy-2-(2-oxo-2,3-dihydro-1*H*-pyrido[2,3-*b*][1,4]thiazin-7-yl)-ethyl]-piperidine-4-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide
- 1-[2-(2,3-Dihydro-[1,4]dioxino[2,3-*c*]pyridin-7-yl)-ethyl]-piperidine-4-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide
- R,S-6-{1-Hydroxy-2-[4-(6-methoxy-[1,5]naphthyridin-4-yloxymethyl)-piperidin-1-yl]-ethyl}-4*H*-benzo[1,4]thiazin-3-one
- 35 R,S-1-[2-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-2-hydroxy-ethyl]-piperidine-4-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide

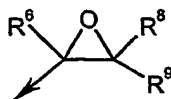
- R,S-1-[2-Hydroxy-2-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl)-ethyl]-piperidine-4-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide
 1-[2-(4-Fluoro-1H-benzimidazol-2-yl)-ethyl]-piperidine-4-carboxylic acid [6-(3-amino-propoxy)-[1,5]naphthyridin-4-yl]-amide
 5 8-{1-[2-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-ethyl]-piperidin-4-ylmethoxy}-2-methoxy-[1,5]naphthyridine
 6-{2-[4-(6-Methoxy-[1,5] naphthyridin-4-yloxymethyl)-piperidin-1-yl]-ethyl}-4H-benzo[1,4]thiazin-3-one
 [(3R,4S)-4-[(6-Methoxy-[1,5]naphthyridin-4-ylcarbamoyl)-methyl]-1-(3-oxo-3,4-dihydro-2H-benzo[1,4]thiazin-6-ylmethyl)-piperidin-3-yl]-acetic acid;
 10 or a pharmaceutically acceptable derivative thereof.

10. A method of treatment of bacterial infections in mammals, particularly in man, which method comprises the administration to a mammal in need of such treatment an effective amount of a compound according to claim 1.
 15 11. The use of a compound according to claim 1, in the manufacture of a medicament for use in the treatment of bacterial infections in mammals.
 20 12. A pharmaceutical composition comprising a compound according to claim 1, and a pharmaceutically acceptable carrier.
 13. A process for preparing a compound according to claim 1, which process comprises reacting a compound of formula (IV) with a compound of formula (V):
 25



- wherein n is as defined in formula (I); Z^{1'}, Z^{2'}, Z^{3'}, Z^{4'}, Z^{5'}, R^{1'}, R^{3'} and R^{4'} are Z¹, Z², Z³, Z⁴, Z⁵, R¹, R³ and R⁴ as defined in formula (I) or groups convertible thereto;
 30 and X and Y may be the following combinations:
 (i) one of X and Y is CO₂RY and the other is CH₂CO₂R^X;
 (ii) X is CHR⁶R⁷ and Y is C(=O)R⁹;
 (iii) X is CR⁷=PR^Z₃ and Y is C(=O)R⁹;

- (iv) X is C(=O)R⁷ and Y is CR⁹=PR^Z₃;
 - (v) one of Y and X is COW and the other is NHR^{11'}, NCO or NR^{11'}COW;
 - (vi) X is NHR^{11'} and Y is C(=O)R⁸ or X is C(=O)R⁶ and Y is NHR^{11'};
 - (vii) X is NHR^{11'} and Y is CR⁸R⁹W;
 - 5 (viii) X is W or OH and Y is CH₂OH;
 - (ix) X is NHR^{11'} and Y is SO₂W;
 - (x) one of X and Y is (CH₂)_p-W and the other is (CH₂)_qNHR^{11'}, (CH₂)_qOH, (CH₂)_qSH or (CH₂)_qSCOR^X where p+q=1;
 - (xi) one of X and Y is OH and the other is -CH=N₂;
 - 10 (xii) X is NCO and Y is OH or NH₂;
 - (xiii) X is CR⁶R⁷SO₂W, A'COW, CR⁶=CH₂ or oxirane and Y is NHR^{11'};
 - (xiv) X is W and Y is CONHR¹¹ or OCONH₂;
- in which W is a leaving group, e.g. halo, methanesulphonyloxy, trifluoromethanesulphonyloxy or imidazolyl; R^X and R^Y are (C₁₋₆)alkyl; R^Z is aryl or (C₁₋₆)alkyl; A' and NR^{11'} are A and NR¹¹ as defined in formula (I), or groups convertible thereto; and oxirane is:



- wherein R⁶, R⁸ and R⁹ are as defined in formula (I);
- 20 and thereafter optionally or as necessary converting A', Z^{1'}, Z^{2'}, Z^{3'}, Z^{4'}, Z^{5'}, R^{1'}, R^{3'}, R^{4'} and NR^{11'} to A, Z¹, Z², Z³, Z⁴, Z⁵, R¹, R³, R⁴ and NR¹¹; converting A-B to other A-B, interconverting R¹, R³ and/or R⁴, and/or forming a pharmaceutically acceptable derivative thereof.

INTERNATIONAL SEARCH REPORT

National Application No

PCT/EP 02/05709

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D471/04 A61P31/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, PAJ, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 00 43383 A (DAVIES DAVID THOMAS ;HENRY CAROLINE JOAN (GB); PEARSON NEIL DAVID) 27 July 2000 (2000-07-27) cited in the application page 1, line 3 -page 1, line 10; claims 1-12; examples 10,11,33 -----	1-13
A	WO 00 21948 A (HATTON IAN KEITH ;PEARSON NEIL DAVID (GB); SMITHKLINE BEECHAM PLC) 20 April 2000 (2000-04-20) cited in the application page 1, line 3 -page 1, line 8; claims 1-12; examples 3-7 -----	1-13



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search

28 August 2002

Date of mailing of the international search report

10/09/2002

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Schmid, A

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-8(partly), 10-13 (partly)

Present claims 1-8 and 9-13 relate to an extremely large number of possible compounds, compositions and methods. In fact, the claims contain so many options, variables and provisos that a lack of clarity (and/or conciseness) within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear and concise, namely compounds, compositions and methods have been searched e.g those compounds recited in the examples (cf. also claim 9) and closely related homologous compounds.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 02/05709

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 10 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.: 1-8(partly), 10-13 (partly)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 02/05709

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0043383	A	27-07-2000	AU 2437900 A WO 0043383 A1 EP 1144404 A1	07-08-2000 27-07-2000 17-10-2001
WO 0021948	A	20-04-2000	AU 6114699 A EP 1127057 A1 WO 0021948 A1	01-05-2000 29-08-2001 20-04-2000